Report From the Workshop on Detection of Potential Toxicities Following Perinatal Exposure to Antiretrovirals

Sponsored by

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Contents

Introduction

In February 1994, AIDS Clinical Trials Group (ACTG) Protocol 076 demonstrated that zidovudine (ZDV) given during pregnancy, labor, and to the newborn could reduce the risk of maternal-fetal HIV transmission by two-thirds. The rapid incorporation of this regimen into clinical practice has been unprecedented, and has been associated with a dramatic decline in perinatal transmission rates to 3 to 5 percent in the United States and other developed countries as well as a significant decrease in the incidence of pediatric AIDS.

Toxicity of this regimen was minimal for both women and infants during ACTG 076. The only significant toxicity observed more frequently in ZDV than placebo recipients was a transient, mild anemia in infants during the period of drug administration that resolved without treatment by age 12 weeks. Subsequent followup of the uninfected infants from this trial in a long-term outcome protocol (ACTG 219) for as long as 5.6 years has not demonstrated differences between those who received ZDV compared to placebo in terms of immunologic, neurodevelopmental, or growth parameters; and no significant organ toxicity or cancers have been seen. The long-term consequences of *in utero* and neonatal antiretroviral drug exposure remain unknown, particularly for the large number of children who will now be uninfected due to ZDV prophylaxis.

ZDV and other nucleoside analogue reverse transcriptase antiretroviral drugs have been found to be mutagenic and carcinogenic in animal tests and *in vitro* studies. There are contradictory animal data on the potential for transplacental carcinogenicity of ZDV.

In one study conducted by National Cancer Institute (NCI) investigators, ZDV was administered to pregnant rodents in daily doses in large excess to those given daily in humans, but which provided a cumulative *in utero* exposure similar to that expected in pregnant women who received 6 months of ZDV antenatally. An excess of liver, lung, and reproductive organ tumors was observed in the offspring of the rodents that received ZDV. Incorporation of ZDV into DNA also was observed in several animal species and in a small number of cord blood samples from infants of infected women who had received ZDV during pregnancy. The significance of this finding is unclear. A potential for transplacental mitochondrial toxicity also was observed in a small primate study. In this study, three patas monkeys received ZDV during pregnancy and their offspring were sacrificed at birth. Histologic abnormalities in fetal tissue mitochondria were seen, as well as functional changes in oxidative phosphorylation enzymes. These changes, however, were not consistent between fetuses.

In contrast, researchers at Glaxo Wellcome performed studies to evaluate transplacental carcinogenic potential in a rodent study designed to mimic human exposure. In these studies, pregnant rodents were given ZDV in doses only approximately 15 to 30 times higher than the daily dose given to humans; offspring also received ZDV postnatally for varying lengths of time. No excess in tumors was observed, with the exception of vaginal tumors in those offspring that also received lifetime ZDV exposure postnatally at the higher dose. Prior studies by Glaxo Wellcome researchers had already documented an increase in vaginal tumors in rodents that had no *in utero* ZDV exposure but that received lifetime high-dose ZDV exposure. It was thought that these vaginal tumors were secondary to vaginal exposure to high concentrations of unmetabolized ZDV excreted in rodent urine that refluxed into the vaginal cavity. In humans,

ZDV excretion is through metabolism to the glucuronide in the liver. Differences between the Glaxo Wellcome and NCI studies include variations in the daily dose administered to the rodents during pregnancy and the doses administered to the offspring.

While the relationship of animal studies to human experience is unclear, the results highlight the importance of continued monitoring for potential long-term toxicity of ZDV prophylaxis, since toxicities related to carcinogenic properties of drugs may not appear until adulthood. Additionally, an increasing number of women are receiving combination antiretroviral regimens including multiple anti-HIV drugs and drug classes in addition to ZDV prophylaxis for prevention of perinatal transmission. Only limited data are available on the short- and long-term toxicities of such combination regimens.

The U.S. Public Health Service has recommended long-term followup for infants with *in utero* and/or neonatal antiretroviral exposure since 1994. From a population-based public health standpoint, this recommendation represents a challenge, because the optimal way to monitor for toxicities has not been well defined, particularly if they are relatively rare. Several possible mechanisms include cohort studies, pharmaceutical registries, and surveillance systems, including the matching of name-based HIV/AIDS surveillance registries with birth defects, cancers, and death registries. Considerations include representativeness, participation, and the need to monitor all exposed children over a long term. The long-term followup may be complicated as HIV-infected mothers become sick; their children may change primary caretakers, geographic residence, health care providers, and their names. Despite challenges for long-term followup, the outstanding confidentiality record and the ability of health departments to locate children whose caretakers have changed suggest that public health mechanisms, as opposed to those sponsored by the pharmaceutical industry, may be the viable mechanisms if scientific evidence suggests it is important to follow up.

In responding to these issues, the National Institutes of Health (NIH) joined with representatives from the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the Health Resources and Services Administration (HRSA) to convene a workshop to (1) review the existing scientific data on potential toxicity of antiretroviral drugs; (2) review the HIV surveillance programs that currently exist that could be used to monitor for such toxicities; (3) examine examples from surveillance for toxicities from other drugs/diseases as models for potential surveillance for antiretroviral toxicity; (4) obtain a community perspective on these issues; and (5) develop recommendations to optimize approaches to detect potential carcinogenicity, birth defects, and/or other toxicities in individuals perinatally exposed to antiretrovirals. Sixty-three clinicians, basic researchers, epidemiologists, and community representatives from the United States and abroad participated in this workshop on January 19-20, 1999, in Bethesda, Maryland. Participants included representatives from academia, industry, and U.S. and foreign governments, as well as consumers and parents of HIV-infected children.

The workshop focused on the following topic areas: (1) Preclinical Studies, (2) HIV Surveillance and Cohort Studies, (3) Community Perspectives, (4) Short-Term Surveillance for Birth Defects, (5) Long-Term Surveillance for Tumors/Cancers, (6) Epidemiology and Statistics, and (7) Setting Up Registries and Cohorts. Participants reviewed seminal journal articles in each of the scientific

topic areas and participated in workshop sessions that included presentations from experts in the focus areas. Workshop participants then divided into three breakout groups that discussed and developed recommendations for the following types of studies:

- Surveillance studies to detect excess risk of birth defects and other neonatal outcomes in infants following perinatal exposure to antiretrovirals;

- Studies to detect excess risk of late malignancies in individuals following perinatal exposure to antiretrovirals; and

- Cohort studies to detect excess risk of developmental/organ toxicities in children and adolescents following perinatal exposure to antiretrovirals.

Rapporteurs were appointed for each breakout group. In a final workshop session attended by all participants, the rapporteurs summarized their respective groups' discussions and presented their groups' recommendations. After final refinements, the rapporteurs drafted the overviews and submitted the recommendations that make up this report. NIH, CDC, FDA, and HRSA will use this document in evaluating, planning, and implementing ongoing and future research and surveillance efforts to assess the short- and long-term effects of perinatal exposure to antiretrovirals. Session summaries have been prepared by CDC and NIH staff for some of the workshop sessions. These summaries are included in Appendix IV.

Addendum

Shortly after this workshop was convened, French researchers reported several pediatric cases, including two deaths, of potential toxicity following perinatal exposure to antiretrovirals. Following these reports, a collaborative group of non-Government researchers and NIH and CDC staff systematically examined the Pediatric AIDS Clinical Trials Group (PACTG), Women and Infants Transmission Study (WITS), Perinatal AIDS Collaborative Transmission Study (PACTS), Pediatric Spectrum of Disease Project, and HIV surveillance databases for any deaths in children born to HIV-infected women related to mitochondrial disease. To date, no deaths have been identified. This group of U.S. experts is currently assessing these databases for symptoms of mitochondrial disorders in living children. These findings underscored that combined evaluation across all existing databases may be needed. This multiagency and multiprogram effort should be considered a model for future investigations. Consideration should be given for expansion of such cross-study analyses to include data from international studies as well.

Additionally, NCI investigators have reported a potential for transplacental mitochondrial toxicity in a small primate study. In this study, three patas monkeys received ZDV during pregnancy, and their offspring were sacrificed at birth. Histologic abnormalities in fetal tissue mitochondria were seen, as well as functional changes in oxidative phosphorylation enzymes. These changes were not consistent between fetuses.

In view of these reports, the Workshop Planning Group proposes that it is important to better define the potential for possible mitochondrial toxicity with perinatal antiretroviral exposure. Thus, they propose that this be included in an expansion of the third recommendation of the Breakout Session on Cohort Studies To Detect Excess Risk of Developmental/Organ Toxicities in Children and Adolescents Following Perinatal Exposure to Antiretrovirals.

Overview and Recommendations on Surveillance Studies To Detect Excess Risk of Birth Defects and Other Neonatal Outcomes in Infants Following Perinatal Exposure to Antiretrovirals

Overview

The Breakout Group discussed surveillance studies to detect excess risk of birth defects and other neonatal outcomes in infants following perinatal exposure to antiretrovirals. It was noted that there was no difference in the incidence of major or minor congenital abnormalities between ZDV and placebo groups in ACTG 076 as well as in the CDC Thailand short-course ZDV prophylaxis trial. To date, there are no data that indicate that administration of ZDV prophylaxis during the last trimester and to the neonate is associated with the development of congenital abnormalities. These placebo-controlled trials did not include drug administration during the first trimester or the use of combination antiretroviral regimens that are increasingly being used to treat HIV-infected pregnant women.

Three specific outcomes were determined to be important and feasible to identify in these studies: major structural birth defects (according to CDC definitions), prematurity, and low birth weight. The ability to determine an association of minor birth defects with antiretroviral exposure was felt to be more limited, but also of lesser relevance, given the significant benefit of ZDV in preventing transmission. Exposure was characterized to include exposure to any antiretroviral agent(s).

As transmission rates continue to decline in the United States due to expanded use of ZDV prophylaxis and possibly as a consequence of an increasing number of women on potent combination regimens during pregnancy, an increasing number of uninfected children will be exposed to potential toxicities of ZDV and other antiretroviral drugs. Children who are followed in observational cohorts and clinical trials will generally be observed through approximately age 6 to 18 months, and detection of adverse birth and neonatal outcomes in such groups should be possible. The detection of events that are rare will require data from large numbers of antiretroviral-exposed individuals, and adverse effects that may occur among children not enrolled in these trials or cohorts also are critical to monitor. CDC estimates that over the next decade approximately 60,000 to 70,000 children will be born to HIV-infected women in the United States. Most of these children will have *in utero* exposure to ZDV and other antiretroviral drugs.

It was recognized that—given the numbers of patients enrolled in current cohorts and clinical trials, as well as limitations in existing surveillance mechanisms—sample size constraints may not permit analyses to have sufficient statistical power to identify small or even moderate associations between antiretroviral drugs and specific birth defects. Additionally, limitations in population size may not permit separation of the effects of antiretrovirals from other potential confounding factors or variables such as disease or other drugs. Innovative mechanisms will be required to enhance existing surveillance mechanisms to enable better delineation of specific risks for adverse pregnancy outcome with antiretroviral drugs.

The Breakout Group concluded that historical controls without antiretroviral exposure may serve as a feasible comparison for children with perinatal antiretroviral exposure. Future studies may be conducted with hypothesis-generated approaches, since observational studies may not provide the

opportunity or venue to test such approaches. While these kinds of studies are less than optimal, the Breakout Group recognized that the findings still would have clinical value to physicians and patients.

The feasibility of new initiatives targeting the issue of birth defects surveillance was discussed in relation to the broad range of drug exposures. Breakout Group members determined they were not able to recommend that additional resources be made available for this effort. It was deemed worthwhile to use existing resources—including data from participants in observational cohorts and randomized clinical trials, as well as HIV surveillance databases that contain perinatal antiretroviral exposure data that can be linked to existing birth defect registries—to try to identify potential relationships between *in utero* antiretroviral exposure and birth defects, prematurity, and low birth weight.

Another mechanism to evaluate potential adverse birth outcomes with antiretroviral exposure is the voluntary Antiretroviral Pregnancy Registry initiated by Glaxo Wellcome and currently maintained by support from the major pharmaceutical companies involved in developing antiretroviral drugs. Through 1998, this registry received prospective data on 647 women who were provided ZDV during pregnancy, and data on 557 live births (290 during the first trimester) were available. No explicit pattern of abnormalities or excess in congenital abnormalities beyond those observed in the general population was observed in the infants of these women. These data are subject to numerous selection biases, followup on birth defects is incomplete, followup on the infants after birth is not included, and the numbers enrolled to date are small.

Recommendations

1. **Explore and improve the New Jersey and New York models of linking HIV surveillance registries that include perinatal antiretroviral exposure data to birth defect registries, and expand these model programs to other States.**

   New Jersey has conducted surveillance for perinatal HIV exposure (with followup to determine HIV infection status, development of AIDS, and death) in addition to pediatric AIDS since 1992. Data on *in utero* and neonatal antiretroviral exposure are routinely collected from both the maternal and the infant medical records. New York State has conducted newborn HIV testing with consent since 1996 and universal newborn HIV testing since 1997. Antiretroviral exposure data also are collected as part of this testing and surveillance program. Both States have received funding from the CDC HIV/AIDS Surveillance Program and the CDC Birth Defects Centers of Excellence to match State birth defect registries with the HIV/AIDS surveillance registries; in New York, matching also will be done with the newborn HIV screening database and the birth defects registry. Expansion of the pilot programs in New Jersey and New York to additional States is strongly recommended. Recommendations with standardized definitions and followup protocols will be needed.

   To more accurately monitor the full public health impact of the epidemic and determine the resources that are required to address it, the CDC, the Council for State and Territorial Epidemiologists, and the American Academy of Pediatrics have recommended that the

surveillance of the HIV epidemic in children be expanded nationwide to include all children with perinatal HIV exposure in addition to children diagnosed with HIV and AIDS. The potential for an emergent public health problem resulting from short- or long-term adverse effects of perinatal exposure to antiretroviral drugs requires such an expansion of perinatal HIV surveillance. Currently, 32 States conduct HIV surveillance, which includes the reporting of perinatal HIV exposure, collection of perinatal antiretroviral exposure data on these children, and followup on each child to determine eventual HIV infection status. Since 1996, data related to birth defects have been added to HIV/AIDS surveillance reports. These registries can be matched to State birth defect registries to evaluate potential teratogenic effects of perinatal antiretroviral exposure, as well as to other registries, such as State death registries. These activities can be done on a State-by-State basis and must be carried out under procedures and policies that maintain high levels of confidentiality and security, which is presently the case with HIV/AIDS surveillance data.

2. **Identify cohorts of exposed individuals from current/future treatment protocols and cohorts, with a subset to be examined rigorously for congenital abnormalities; strongly consider expansion of ACTG 219 to include infants born to women who receive antiretroviral drugs outside of perinatal treatment protocols.**

   Consideration should be given to having a subset of children in current prospective longitudinal protocols and/or other prospective cohorts (such as the WITS and PACTS) evaluated in a rigorous manner for the presence of major congenital abnormalities.

   ACTG 219 is a prospective longitudinal study of late outcomes of children from the ACTG 076 trial and other PACTG perinatal/neonatal clinical trials in which the infant is exposed to antiretroviral drugs either *in utero* or neonatally. The study provides standardized followup of these children through age 21 years and includes uninfected as well as infected children. Although this study includes in-depth longitudinal observations, the numbers of children enrolled will likely not permit assessment of the association of any relatively rare outcome with antiretroviral exposure. It is recommended that consideration be strongly given to expansion of ACTG 219 to enroll infants at PACTG sites who are born to the larger number of HIV-infected women who receive antiretroviral therapy outside of traditional perinatal clinical trials; this would enable standardized and systematic followup of larger numbers of antiretroviral-exposed infants.

3. **Encourage the FDA to promote postmarketing surveillance registries for antiretroviral drugs administered during pregnancy (e.g., potentially require such activities for antiretroviral drugs that may be administered in pregnancy); continue and improve the existing collaborative pharmaceutical company Antiretroviral Pregnancy Registry.**

4. **Utilize and expand case-control surveillance, as is currently conducted by the CDC Birth Defects Centers of Excellence, to evaluate the association of perinatal antiretroviral drug exposure to birth defects.**

5. **Consider data and experience from sources outside of the United States, and explore international collaborations.**

Overview and Recommendations on Studies To Detect Excess Risk of Late Malignancies in Individuals Following Perinatal Exposure to Antiretrovirals

Overview

The Breakout Group discussed the optimal methods to detect an excess risk of late malignancies in individuals perinatally exposed to antiretroviral agents. Group members recognized that such cancers would likely be relatively rare events involving small numbers of individuals; hence, an effective surveillance system will require an extremely large database.

The Breakout Group also noted that it may take several decades before these malignancies could develop and be observed, as is the case of human T-cell lymphotrophic virus type I (HTLV-I)-related adult T-cell lymphoma/leukemia (ATLL). ATLL develops in less than 5 percent of HTLV-I-infected individuals with a latency of 30 to 40 years. Thus, long periods of followup may be necessary in order to detect late malignancies following perinatal exposure to antiretrovirals. Furthermore, specific surveillance mechanisms will be needed to detect excess risk of late malignancies. The need to use retrievable unique identifiers (e.g., name and Social Security number) was discussed, given the length of time from neonatal exposure to the detection of possible late malignancies in middle age.

It is important to recognize that any potential toxicity of perinatal antiretroviral exposure must be compared to the known benefits of ZDV for prevention of perinatal transmission of HIV, a life-threatening disease. In order to design a study or surveillance system to detect whether an excess cancer risk is associated with perinatal antiretroviral exposure, it is first critical to determine what level of relative increase in cancer risk is important to detect from a public health perspective. This is necessary to determine the number of individuals that would need to be included in such a study or surveillance mechanism to have adequate power to definitively address the question of risk.

The utility of both "exposure-based" studies as well as "outcome-based" studies was discussed in terms of evaluation of whether there is an association of perinatal antiretroviral exposure with malignancy. "Exposure-based" studies include those that have a universal database of antiretroviral exposure with followup for potential outcomes over time, whereas "outcome-based" studies include those databases that track malignancies and use the database to determine whether there is an excess of certain malignancies that could be associated with antiretroviral exposure. For both types of studies, databases that contain reliable information related to perinatal antiretroviral exposure as well as malignancy incidence are essential.

The Breakout Group concluded that conducting surveillance studies linking perinatal antiretroviral exposure registries to cancer registries was the optimal method to assess the potential long-term risk of malignancies associated with such exposure. It was noted that some, but not all, of the States in the United States are currently collecting HIV/AIDS surveillance data (see previous section on birth defects). Perinatal antiretroviral exposure registries could then be linked to cancer registries. It was noted that for detection of risk for "early" cancers (e.g., during childhood or adolescence), it may be necessary to develop national pediatric and adolescent cancer registries, as these currently exist only at the State level.

The Breakout Group concluded that cancer risk in persons with *in utero* antiretroviral exposure should be evaluated in a time-dependent manner and broken down into different age-related endpoints. The ability and feasibility of obtaining valid information related to cancer risk in different age groups may vary, with the shorter-term cancer risk (e.g., childhood cancers) likely to be more readily definable. Age-related grouping suggested included the following:

- Childhood cancer risk (e.g., 10- to 13-year window)
- Adolescent cancer risk (e.g., 15- to 20-year window)
- Adult cancer risk (e.g., requires prolonged followup for 30-40+ years)

For assessment of risk for childhood and adolescent cancer, the development of a national pediatric and adolescent cancer registry/database may be required and should be considered by agencies funding such surveillance.

Breakout Group members concluded that further basic scientific research is needed on the mechanisms involved in the development of malignancies, the development of appropriate animal models, and the identification of exposure markers. They also suggested that, if the relative risk of malignancies increases, other factors may need to be examined—such as the role of paternal antiretroviral drug use—and new epidemiologic methods may need to be developed for evaluating long-term risk. Group members strongly emphasized that it was essential that the affected community be involved in planning for the conduct of long-term surveillance programs.

Recommendations

1. **Consideration should be given to providing dedicated funds to all States to expand HIV/AIDS surveillance to include perinatal HIV exposure on a national basis, and to include collection of perinatal antiretroviral exposure data.**

   These recommendations are similar to those made by the Birth Defects Surveillance Group. Surveillance linkage of perinatal antiretroviral exposure registries to cancer registries will be important, but currently only 32 States conduct perinatal HIV exposure data. It is recommended that funding for resources to collect such data be made available for all States for this purpose. Such data will provide the only population-based evaluation of perinatal antiretroviral exposure to enable studies to be conducted that could determine on a population basis the risk for specific adverse outcomes of such exposure, including cancer.

   Michigan and New Jersey, which both conduct perinatal HIV exposure surveillance, are currently performing a pilot project to match perinatal HIV surveillance registries with State cancer registries.

2. **Consideration should be given to augmentation of funding for existing perinatal cohorts (e.g., the NIH-sponsored ACTG 076/219 and WITS and CDC-sponsored PACTS) to enable continued in-depth, standardized followup of specific cohorts of uninfected infants who have had perinatal antiretroviral exposure**.

WITS and PACTS are two large ongoing cohorts in the United States that are following large numbers of children born to HIV-infected pregnant women; WITS is currently continuing enrollment, whereas PACTS recently closed enrollment of new patients. These studies include infants both with and without antiretroviral exposure, and therefore also provide important comparison populations for future case-control studies. There has been a decrease in the amount of followup provided for uninfected infants to enable conservation of resources targeted toward questions related to infected children. Augmented funding to ensure continued followup of the large number of uninfected children in these studies should be strongly considered.

3. **The potential development of new cohorts or new innovative approaches to long-term followup should be considered by funding agencies.**

   For example, consideration might be given to evaluating the utility of simple followup mechanisms that include large numbers of patients (e.g., a yearly query card to providers requesting information related to a specific serious outcome such as cancer).

4. **A national standardized registry for cancer in children and adolescents is critically needed; possible international collaboration on such a registry would be desirable.**

   It is recommended that CDC consider convening a meeting to discuss the process and strategies for the development and implementation of pediatric/adolescent cancer registries. The possibility of international collaboration should be considered.

5. **Develop a unique "identifier" system that would enable matching individuals with perinatal antiretroviral exposure to other registries. Such an identifier must be feasible, retrievable, and acceptable to the affected community (e.g., Social Security numbers versus some other unique identifiers).**

   As public health officials develop the optimal approach, the issues related to confidentiality are critical, and input from representatives of the affected community regarding the best way to conduct such surveillance should be considered. Model laws also will be important, as they define who has access to the information and for what purpose as well as what the penalties are for unauthorized use.

6. **NIH should convene a meeting to discuss basic scientific studies that must be performed in this area and to make recommendations.**

   A meeting of basic scientists to develop recommendations for future research should be considered by NIH, with the development of funding strategies to ensure that the highest priority scientific questions are addressed (e.g., possible development of a Request for Applications targeted to stimulating research in this area).

7. Additional funding of critical basic scientific studies is urgently needed.

Critical basic science studies discussed by the Breakout Group included the following:

- Animal models studies to evaluate *in utero* exposure to antiretroviral combination regimens as well as monotherapy regimens. Multiple species should be studied, including primates when possible.

- Studies to elucidate the biomarkers of exposure. Objectives include the following:

  - Evaluate the length of time ZDV-DNA adducts exist and what the factors are that influence this process (e.g., phosphorylation, the incorporation of drugs into DNA, and DNA repair, which influence the ability to excise drugs from affected DNA strands);

  - Assess pharmacogenetic influences on the potential for carcinogenicity; and

  - Evaluate better biomarkers of exposure that could be monitored in an individual over time to predict risk.

- Studies to better understand DNA repair mechanisms. Objectives include the following:

  - Evaluate the mechanisms used to repair DNA damaged by incorporation of chain-terminating drugs;

  - Determine whether these repair mechanisms are saturable at the rates of chain-terminator incorporation that occur following exposure to clinically meaningful antiretroviral drug concentrations (as opposed to concentrations far in excess of what would be achieved with clinical exposure); and

  - Determine whether there is a "threshold" effect in terms of DNA repair mechanisms for DNA damaged by incorporation of chain terminator drugs.

8. The Department of Health and Human Services should make sure that appropriate Federal agencies convene a meeting with representatives from health care providers, public health agencies, and the affected community to discuss and provide recommendations related to long-term surveillance of perinatally exposed individuals.

Overview and Recommendations on Cohort Studies To Detect Excess Risk of Developmental/Organ Toxicities in Children and Adolescents Following Perinatal Exposure to Antiretrovirals

Overview

The Breakout Group addressed the use of cohort studies for the detection of excess risk of developmental/organ toxicities in children and adolescents following perinatal exposure to antiretrovirals. The use of existing cohort studies was considered preferable to population-based registries for linkages of fetal/neonatal antiretroviral exposure and outcome, although a role for surveillance databases to potentially supplement more detailed investigations also was acknowledged and discussed.

Breakout Group members developed the accompanying table (Table 1) to summarize some of the specific outcomes—e.g., growth failure, developmental delay, abnormal pubertal development, and other organ system toxicity—that are currently being followed in NIH- and CDC-funded cohorts and clinical trials. They noted the long-term followup of children will be complicated by parental death and child placement, which may result in change in geographic residence, health care provider, or even the child's name.

Table 1

Outcomes Followed in NIH and CDC Cohorts and Clinical Trials		
Outcome	**Studies**	**Length of Followup Needed**
Growth Failure	PACTG 219 WITS PACTS	3 to 5 years
Abnormalities in Pubertal Development	PACTG 219 WITS PACTS	18 to 21 years
Neurodevelopment (developmental delay)	PACTG 219 WITS PACTS	Not determined, but would require followup into school age and include assessment of school performance
Other Organ Toxicities (cardiac, liver, renal, central nervous system, other)	PACTG 219 WITS	Not determined, but at least through age 5 years

The issues of confidentiality and use of identifiers for registries also were discussed, since the Breakout Group recognized that cohort study participants would need to be followed from infancy through adolescence. The Breakout Group noted that unique identifiers are needed to establish a functional registry and that linkage to participants' names must be secure, as participant confidentiality is essential. As noted in previous breakout sessions, involvement of the affected community was deemed critical to developing and maintaining all registries.

Recommendations

1. **Better utilize existing cohorts and HIV/AIDS surveillance mechanisms to assess potential associations of perinatal antiretroviral exposure to developmental/organ toxicities and other outcomes; this may require augmented funding of selected ongoing studies.**

   As noted in previous Breakout Group reports, PACTS and WITS are large U.S. prospective studies that follow children born to HIV-infected pregnant women. WITS is currently enrolling new patients, while PACTS has stopped enrollment. These studies include infants both without and with antiretroviral exposure. In addition to providing standardized, systematic followup for children with antiretroviral exposure, these studies also provide important historical comparison populations for case-control studies. However, followup of uninfected infants has been curtailed in both studies due to limitations in resources. Consideration should be given to augmenting funding for these studies to include (and in the case of PACTS, restart) followup of uninfected, antiretroviral-exposed infants for longer periods of time to evaluate potential long-term adverse consequences.

   ACTG 219, the long-term outcome protocol discussed in previous sections, is limited by the current restriction of enrollment to infants born to women who have participated in PACTG perinatal trials or who have participated in neonatal antiretroviral trials. The utility of this database would be significantly improved if enrollment could be expanded to include all infants born to infected women who have received antiretroviral therapy during pregnancy, regardless of perinatal trial enrollment. Additional funding to PACTG sites will likely be required to accomplish broader enrollment.

   ACTG 219 or a simplified modification might be utilized to provide a standardized followup for children in non-PACTG, HRSA-funded Title IV sites. Development of a standard database with such followup data would provide important supplementary information to the more detailed evaluations performed as part of prospective cohort studies or ACTG 219.

   HIV surveillance databases, such as the Pediatric Spectrum of Disease (PSD) Project and the HIV/AIDS surveillance database, also may provide useful information regarding at least short-term adverse toxicities. In these studies, information is collected on uninfected children through the time of definitive diagnosis, at which point continued followup of uninfected children is stopped. More prolonged followup of such uninfected infants through these surveillance projects may also be considered.

2. **As noted in prior Breakout Group reports, it is critical to address issues related to the requirement for unique identifiers.**

   The Breakout Group discussed the need to (1) emphasize good science in the identification of acceptable identifiers and the legal issues of data access and uses, (2) ensure confidentiality (encryption), and (3) encourage model State law adoption (e.g., model legislation that could be provided to States related to violations in confidentiality/security of surveillance data).

Consultation with community representatives regarding use of identifiers is important in developing plans for surveillance-based studies.

3. **Continue and expand animal studies to address research issues related to potential organ toxicity (e.g., the relationship to perinatal antiretroviral exposure to specific toxicities, examining time of onset, duration, and permanence of such toxicity after antiretroviral exposure has stopped). Consultation with basic science experts to better define the high-priority studies should be considered (see recommendations in the Malignancy Breakout Group section).**

4. **Identify international collaborators for participation in standardized studies to evaluate late toxicities and/or to collaborate in meta analyses.**

5. **Consider expanding ACTG 219 to Title IV grantees and their clients.**

6. **Increase collaboration with Title IV grantees in the evaluation of potential toxicities.**

Appendix I

National Institutes of Health

Workshop on Detection of Potential Toxicities
Following Perinatal Exposure to Antiretrovirals

January 19–20, 1999

Hyatt Regency Bethesda
One Bethesda Metro Center
Bethesda, Maryland 20814

AGENDA

Tuesday, January 19, 1999 ***Morning Session***

8:30	Introduction and Goals of the Meeting	*Dr. Neal Nathanson* *Office of AIDS Research, NIH*

I. BACKGROUND INFORMATION

SESSION 1: PRECLINICAL STUDIES
Moderator: Dr. Lynne Mofenson
National Institute of Child Health and Human Development, NIH

8:40	Transplacental Effects of AZT: Tumorigenicity in Mice and Genotoxicity in Mice and Monkeys	*Dr. Miriam C. Poirier* *National Cancer Institute, NIH*
8:55	Glaxo Wellcome AZT Transplacental Tumorigenicity Study	*Dr. Ken Ayers* *Glaxo Wellcome, Inc.*
9:10	Transplacental Mutagenicity of AZT in Rodents: Planned Studies	*Dr. Vernon Walker* *New York State Department of Health*
9:25	Transplacental and Perinatal Toxicity of Antiretrovirals: A Summary of Preclinical Findings	*Dr. James G. Farrelly* *Food and Drug Administration*
9:40	Questions and Answers	
10:10	**BREAK**	

SESSION 2: HIV SURVEILLANCE AND COHORT STUDIES
Moderator: Dr. Mary Glenn Fowler
National Institute of Allergy and Infectious Diseases, NIH

10:25	Overview—CDC's Perinatal AIDS Collaborative Transmission Study	*Dr. Marc Bulterys* *Centers for Disease Control and Prevention*
10:40	ACTG 076 and ACTG 219	*Ms. Mary Culnane* *National Institute of Allergy and Infectious Diseases, NIH*
10:55	The Women and Infants Transmission Study (WITS) and Combination Antiretroviral Data	*Dr. Ruth Tuomala* *Brigham and Women's Hospital*
11:10	Pediatric HIV/AIDS Surveillance	*Dr. Mary Lou Lindegren* *Centers for Disease Control and Prevention*
11:25	Tampa Bay's Pediatric Antiviral Exposure Study	*Dr. Patricia Emmanuel* *CMS Referral Center* *and Ms. Nora Shively* *Florida Family AIDS Network*
11:40	Questions and Answers	
12:10	**LUNCH**	

Tuesday, January 19, 1999 ***Afternoon Session***

SESSION 3: COMMUNITY PERSPECTIVES
Moderator: Dr. Deborah Parham
Health Resources and Services Administration

1:10	Mother/Consumer Perspective 1	*Ms. Rebecca Denison* *WORLD*
1:25	Mother/Consumer Perspective 2	*Ms. Carla Cunningham* *Children's Diagnostic and Treatment Center*
1:40	Questions and Answers	

II. STRATEGIES AND APPROACHES CURRENTLY IN USE FOR SURVEILLANCE OF POPULATIONS EXPOSED TO POTENTIAL TOXICANTS

SESSION 4: SHORT-TERM SURVEILLANCE FOR BIRTH DEFECTS

Moderator: Dr. Larry Edmonds
Centers for Disease Control and Prevention

2:00	Overview	*Dr. Larry Edmonds*
2:15	Antiviral Drug Registries for Birth Defects	*Dr. Alice White* *Glaxo Wellcome, Inc.*
2:35	The Role of the Clinician for Identification of Potential Syndromes: Historical Perspective of Fetal Alcohol Syndrome	*Dr. Kenneth L. Jones* *University of California, San Diego*
2:55	Overview of Other Registries and Approaches	*Dr. Allen A. Mitchell* *Boston University*
3:15	Questions and Answers	
3:45	**BREAK**	

SESSION 5: LONG-TERM SURVEILLANCE FOR TUMORS/CANCERS

Moderator: Dr. James J. Goedert
National Cancer Institute, NIH

4:00	Diethylstilbestrol (DES) Followup	*Dr. Arthur Herbst* *University of Chicago*
4:15	CDC's National Cancer Registry	*Dr. Daniel S. Miller* *Centers for Disease Control and Prevention*
4:30	AIDS/Cancer Matches Registry	*Dr. Robert J. Biggar* *National Cancer Institute, NIH*
4:45	Childhood AIDS/Cancer Followup	*Dr. H. Stacy Nicholson* *Oregon Health Science University*
5:00	CDC Agency for Toxic Substances and Disease Registry	*Dr. Je Anne Burg* *Centers for Disease Control and Prevention*
5:15	England's Registry	*Dr. Catherine S. Peckham* *Institute of Child Health, UK*
5:30	Questions and Answers	
6:00	**ADJOURN FOR THE DAY**	

III. METHODOLOGIC AND PRACTICAL ISSUES IN IMPLEMENTING SURVEILLANCE AND COHORT STUDIES TO DETECT POTENTIAL AND/OR DELAYED TOXICITIES

SESSION 6: EPIDEMIOLOGY AND STATISTICS

Goal of Session: Provide the workshop participants, representing a wide range of technical and scientific expertise, with the basic epidemiologic tools and concepts needed to discuss implementing surveillance and cohort studies to detect potential and/or delayed antiretroviral toxicities.

Moderator: Dr. Sandra Melnick
National Cancer Institute, NIH

8:00	Basic Epidemiologic Concepts	*Dr. Guthrie Birkhead* *New York State Department of Health*
8:30	Statistical Issues (Samples Sizes, Control Groups, and Analytical Approaches)	
	• Surveillance Studies	*Dr. Philip L. Rhodes* *Centers for Disease Control and Prevention*
	• Cohort Studies	*Dr. Alvaro Munoz* *Johns Hopkins University*
9:30	Questions and Answers	
9:45	**BREAK**	

SESSION 7: SETTING UP REGISTRIES AND COHORTS

Moderator: Dr. Martha Rogers
Centers for Disease Control and Prevention

10:00	Confidentiality, Ethical, and Legal Issues	*Dr. Zita Lazzarini* *University of Connecticut Health Center* *and Dr. James G. Hodge, Jr.* *Georgetown Law School*
10:20	Experiences of State HIV/AIDS Registries	
	• New Jersey Department of Health and Senior Services	*Dr. Sindy Paul*
	• New York State Department of Health	*Dr. Guthrie Birkhead*
	• Michigan Department of Community Health	*Dr. Eve Mokotoff*
11:05	Using Administrative Data To Assess AZT Use and Birth Defects	*Dr. Craig Newschaffer* *Thomas Jefferson University*
11:20	Questions and Answers	

11:30 **LUNCH**

Wednesday, January 20, 1999 ***Afternoon Session***

IV. DEVELOPMENT OF STUDY RECOMMENDATIONS

Moderator: Dr. Allen A. Mitchell
Boston University

12:30 Charge to the Breakout Groups — *Dr. Allen A. Mitchell*

SESSION 8: BREAKOUT GROUP DISCUSSIONS

12:45 Group A: Surveillance Studies To Detect Excess Risk of Birth Defects and Other Neonatal Outcomes in Infants Following Perinatal Exposure to Antiretrovirals

Group Chair: *Dr. Howard Minkoff, Maimonides Medical Center*
Rapporteur: *Dr. Allen A. Mitchell*
Presenter: *Dr. Nancy Wade, New York State Department of Health*

Group B: Surveillance Studies To Detect Excess Risk of Late Malignancies in Individuals Following Perinatal Exposure to Antiretrovirals

Group Chair: *Dr. William A. Blattner, Institute of Human Virology*
Rapporteur: *Dr. Alexandra M. Levine, University of Southern California*
Presenter: *Dr. Brad Pollock, University of Florida College of Medicine*

Group C: Cohort Studies To Detect Excess Risk of Developmental/Organ Toxicities in Children and Adolescents Following Perinatal Exposure to Antiretrovirals

Group Chair: *Dr. Patricia Whitley-Williams, Robert Wood Johnson Medical School*
Rapporteur: *Dr. Celine I. Hanson, Baylor College of Medicine*
Presenter: *Dr. Catherine Wilfert, Pediatric AIDS Foundation*

2:45 **BREAK**

3:00 Group Reports and Recommendations

Group A Rapporteur: *Dr. Allen A. Mitchell*

Group B Rapporteur: *Dr. Alexandra M. Levine*

Group C Rapporteur: *Dr. Celine I. Hanson*

4:00 Closing Remarks — *Dr. Neal Nathanson*

ADJOURN

Appendix II

Workshop on Detection of Potential Toxicities Following Perinatal Exposure to Antiretrovirals

January 19–20, 1999

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Appendix III

Journal Articles Reviewed by Workshop Participants

SESSION 1: PRECLINICAL STUDIES

Vaginal Epithelial DNA Damage and Expression of Preneoplastic Markers in Mice During Chronic Dosing with Tumorigenic Levels of 3'-Azido-2',3'-Dideoxythymidine. Olivero OA, Beland FA, Fullerton NF, and Poirier MC, *Cancer Res*. 1994 Dec 1;54(23):6235-42.

AZT, A Genotoxic Transplacental Carcinogen in Rodents, Is Incorporated into Human Fetal and Maternal DNA. Olivero OA, Chougnet C, Shearer GM, Kovacs A, and Poirier MC. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1998 Apr 1;17(4):A1-43.

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SESSION 7: SETTING UP REGISTRIES AND COHORTS

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Appendix IV

Background Summaries of Workshop Presentations

SESSION 1: PRECLINICAL STUDIES

Moderator: Dr. Lynne Mofenson
National Institute of Child Health and Human Development, NIH

Transplacental Effects of AZT—National Cancer Institute (NCI) Studies

Dr. Miriam C. Poirier
National Cancer Institute, NIH

Dr. Poirier described transplacental effects of *in utero* high-dose azidothymidine (AZT) or exposure in animals in terms of potential tumorigenicity, genotoxicity, and mitochondrial myotoxicity.

Tumorigenicity

In utero exposure: Pregnant mice were given 0 (control), 12.5, and 25 mg of AZT per day from day 12-18 of gestation and their progeny were examined. In necropsies at 1 year, a dose-related increase over controls was observed for lung tumors in male and female pups, liver tumors in males, and female reproductive organ tumors (published in the *Journal of the National Cancer Institute)*. In necropsies at 2 years, a dose-related increase over controls was again noted for lung tumors in male and female pups, liver tumors in males, and reproductive organ tumors in both males and females. The reproductive organ tumors included mammary adenocarcinoma (0 in controls, 2 percent and 6 percent in lower and higher dose AZT, respectively); ovarian tumors (0 in controls, 4 percent and 8 percent in lower and higher dose AZT, respectively); and seminal vesicle tumors (0 in controls, 0 percent and 5.5 percent in lower and higher dose AZT, respectively).

Neonatal exposure: Neonatal mice were given 25, 50, 100, and 200 mg/kg of AZT per day by injection from postnatal days 1-8. An increase in lung, liver, and mammary tumors in females only was observed, with a dose-related increase in the number of tumors per animal.

Genotoxicity

AZT incorporation into DNA: A radioimmunoassay was used to detect AZT incorporation into DNA in mice, patas monkeys, rhesus monkeys, and cord blood from humans. AZT was found to be incorporated into DNA in all four species studied.

Mitochondrial Toxicity

Pregnant patas monkeys were given doses of 10 mg and 40 mg of AZT per day (equivalent to approximately 10 percent and approximately 80 percent of exposure in humans). Fetal tissue was obtained at cesarean section, and transmission electron microscopy was performed, as were assays for mitochondrial oxidative phosphorylation electron transport enzyme complexes 1-4. At the lower dose, cardiac muscle tissue mitochondria were swollen with membrane rupture and decreased cristae; at higher dose, vacuous cytoplasm and abnormal mitochondrial shape were seen. Nicotinamide adenine dinucleotide (NADH) dehydrogenase was found to be decreased in a dose-dependent manner in placenta, fetal heart, and skeletal tissue.

Summary

These studies administered AZT in daily doses in great excess to those given daily in humans, but provided a cumulative *in utero* AZT exposure similar to that expected in pregnant women who received 6 months of AZT antenatally. Transplacental carcinogenicity was observed, with excess of liver, lung, and reproductive organ tumors in mice pups. AZT incorporation into DNA was observed in several animal species and in some cord blood samples from infants of infected women who had received AZT during pregnancy. A potential for mitochondrial toxicity was observed in a small number of one species of primate.

Transplacental Effects of AZT—Glaxo Wellcome Studies

Dr. Ken Ayers
Glaxo Wellcome, Inc.

Dr. Ayers reported on the nonclinical toxicology studies of AZT in animals performed by Glaxo Wellcome, and on the transplacental effects of *in utero* AZT exposure in mice at much lower daily doses than used in Dr. Poirier's study related to tumorigenicity.

Nonclinical Toxicology Studies of AZT in Animals

The following results were observed in nonclinical toxicology studies of AZT: reversible macrocytic anemia in rats and monkeys in 3-, 6-, and 12-month studies; no effect on fertility in males or females; no teratogenicity except at extremely high doses (3,000 mg/kg/day) near the maximum lethal dose in female animals (3,683 mg/kg/day); early embryonal toxicity in mice at 150 or 450 mg/kg/day and late fetal toxicity in the rabbit at 500 mg/kg/day; positive screening tests for mutagenesis and clastogenesis; and late-appearing squamous cell carcinoma of the vagina in rats dosed at 300 mg/kg/day and mice dosed at 30 or 40 mg/kg/day.

In Utero and Postpartum Pup Exposure

In these studies, AZT was administered not just during gestation but also to the pups for varying lengths of time. These studies used significantly lower doses than evaluated in the previous studies described by Dr. Poirier. Two control groups consisted of an environmental control and vehicle control. The low-dose group of pregnant mice received 20 mg/kg/day AZT from gestation day 10 through lactation day 21 with continued administration of this dose for 24 months to the pups. Three high-dose groups of pregnant mice received AZT 40 mg/kg/day from gestation day 10 through lactation day 21; one group of pups received this dose of AZT for 24 months; another for 90 days; and the last group of pups received no postnatal AZT.

Histopathologic examination of the mice at 24 months found no increase in tumors in either male or female mice compared to control with the exception of squamous cell carcinomas (as was previously observed in the nonclinical toxicology studies) which occurred only in the three groups of pups that received postnatal as well as *in utero* AZT exposure, with the highest incidence of vaginal tumors in the pups in the high-dose postnatal 24-month exposure group. The incidence of tumors in these pups with *in utero* plus lifetime exposure (approximately 16 percent) was not observed to be significantly higher than the incidence in mice with only postnatal exposure (approximately 12 percent).

Pharmacokinetic studies were done to evaluate peak levels of drug in these animals as compared to human exposures. The human C_{max} with a 300 mg oral dose is 1.6 Fg/mL; in the 20 mg/kg mouse group, C_{max} was 15 Fg/mL; and in the 40 mg/kg mouse group, the C_{max} was 37 Fg/mL.

Summary

These studies were designed to mimic human exposure but with AZT dosing to produce levels approximately 15 to 30 times higher than in humans. No transplacental tumorigenicity was

observed over and above the previously noted vaginal tumors with lifetime exposure in animals without *in utero* exposure. Differences between the Glaxo Wellcome and NCI studies include daily dose administered as well as exposure of the pup to drug.

Transplacental Effects of AZT—Planned Studies

Dr. Vernon Walker
New York State Department of Health

Dr. Walker reviewed his ongoing studies on *in utero* exposure to AZT and other antiretroviral (ARV) drugs. He is using a set of molecular biomarkers of dose and effect to evaluate the potential of AZT to act as a transplacental clastogen/mutagen at therapeutic doses in rodents and humans and to produce biological data in rodent studies that will improve the assessment of long-term genetic risks of *in utero* AZT exposure.

Hypotheses being tested include the following:

1. Detectable levels of AZT are incorporated into DNA in tissue of rodents and humans exposed *in utero* or as neonates.

2. This AZT treatment is clastogenic and mutagenic in rodents and humans.

3. Treatment of rodents *in utero* at doses of AZT similar to the cumulative dose a pregnant woman would receive induces species-specific types of cancer in rats and mice.

4. These genotoxic and tumorigenic effects of AZT are dose related.

5. The potential of AZT to produce mutagenic and carcinogenic effects is primarily dependent on its bioavailability for bioactivation, which is governed in an individual by the extent of AZT glucuronidation.

He plans to study the following:

- Markers of exposure: Incorporation of AZT into DNA in tissues of rodents and infants.
- Biomarkers of effect: Chromosomal abnormalities in rodents and infants; frequency and nature of mutations in glycophorin A, hypoxanthine phosphoribosyl-transferase (HPRT), and thymidine kinase genes in infants (taking into account confounders such as maternal smoking, drug use, etc.).
- Biomarkers of sensitivity: Plasma levels of glucuronide (GAZT):AZT and AZT-monophosphate:AZT ratios and AZT monophosphate, diphosphate, and triphosphate levels; cellular anabolic enzyme activities (involved in phosphorylation of AZT to triphosphate).

Rodent Studies

Three species (CD1 and B6C3F1 mice and F344 rats) will be studied. Pregnant mice will receive AZT from days 12-18 gestation and pregnant rats from days 15-21 gestation at doses 0 (control), 40, 240, or 280 mg/kg/day. These regimens will provide a cumulative exposure to AZT of 0, 280, 1,680, and 3,360 mg/kg, respectively. This compares with cumulative AZT exposure with 6 months of AZT in a pregnant woman of approximately 1,600 mg/kg. Necropsies will be performed on pups at 1 year (320 mice, 320 rat pups) and at 2 years (600 mice, 480 rats) to evaluate them for tumor development. These studies will evaluate AZT incorporation into tissues immediately after birth, the "time course" of genotoxic biomarker appearance and dose response of such markers, and potential germ cell genotoxicity in male pups.

Human Studies

The following groups will be evaluated:

Group 1:	Infants born to infected women receiving AZT/ARV therapy (N=70).
Group 2:	Infants born to infected women who did not receive AZT/ARV therapy antenatally (N=70), with subgroups: • Infants that did not receive AZT/ARV therapy. • Infants that received AZT/ARV therapy.
Group 3:	Infants born to uninfected women (N=70).

The sample size will permit detection of a one-and-a-half to twofold increase in mutant frequency (glycophorin A and/or HPRT) in infants with *in utero* AZT exposure.

Cord blood, umbilical cord, and blood samples will be obtained from all infants at 52 weeks of age; the subset of infants in Group 2 also will have blood samples taken at 6 weeks. Specimens from a subgroup of infants at one site where special immediate processing of umbilical cord samples can be done will be evaluated by electron microscopy to evaluate potential mitochondrial damage. To evaluate for potential maternal confounders, a maternal hair sample will be taken and assessed for cocaine, heroin, and cotinine (a measure of cigarette smoking).

Summary

These studies are ongoing, and the human studies have not yet completed enrollment. It is anticipated that preliminary data may be available during 1999.

Transplacental and Perinatal Effects of ARV Therapy—Summary of Preclinical Data

Dr. James G. Farrelly
Food and Drug Administration (FDA)

Dr. Farrelly reviewed the types of preclinical studies required by the FDA and briefly reviewed data on the currently available ARV therapy.

Preclinical Study Types

Segment 1 studies assess effects on fertility and early embryo development.

Segment 2 studies assess teratogenicity.

Segment 3 studies assess perinatal effects.

FDA Categories

A. No risk to fetus; adequate and controlled studies in women. Of all approved drugs as a whole, only six drugs have this category.

B. Animal or human studies fail to show fetal risk; no adequate/controlled studies in women.

C. Adverse effect on fetus in animal studies or animal studies not performed. Approximately 50 percent of available drugs have had no testing performed and are in this category.

D. Positive evidence of human fetal risk but potential drug benefit for woman (a warning is indicated in the product label).

X. Teratogenic risk is greater than benefit.

Table 1

Data on Specific Antiretroviral Drugs/Classes: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Drug	**Pregnancy Category**	**Date Approved**
AZT	C	3/87
ddI	B	10/91
ddC	C	6/92
d4T	C	6/94
3TC	C	11/95
Abacavir	C	12/98

Summary

All NRTIs are genotoxic in a number of different tests, as expected by their mechanism of action. AZT, ddC, and d4T in high doses are carcinogenic in 2-year animal assays; 3TC and ddI are not; abacavir has not been studied. All but ddI are category C.

Table 2

Data on Specific Antiretroviral Drugs/Classes: Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Drug	**Pregnancy Category**	**Date Approved**
Nevirapine	C	6/96
Delavirdine	C	4/97
Efavirenz	C	9/98

Summary

None of the NNRTIs are genotoxic on screening tests. All are being studied in carcinogenicity studies that are not yet completed. All are category C. Delavirdine is a teratogen in rats. Efavirenz induced malformations in monkeys—3 of 20 fetuses born to monkeys receiving drug during pregnancy had central nervous system malformations (e.g., microencephaly, microphthalmia, cleft palate).

Table 3

Data on Specific Antiretroviral Drugs/Classes: Protease Inhibitors		
Drug	**Pregnancy Category**	**Date Approved**
Saquinavir	B	12/95
Ritonavir	B	3/96
Indinavir	C	3/96
Nelfinavir	B	3/97

Summary

None of the protease inhibitors are genotoxic on screening tests. Carcinogenicity studies have not been completed on these drugs. All but indinavir are category B. Indinavir was classified as category C due to concerns related to hyperbilirubinemia in the neonate—when given in the third trimester to pregnant rhesus monkeys, indinavir was not associated with hyperbilirubinemia in neonates; however, when given to neonatal monkeys, physiologic hyperbilirubinemia was exacerbated, with bilirubin levels increased approximately fourfold.

SESSION 2: HIV SURVEILLANCE AND COHORT STUDIES

Moderator: Dr. Mary Glenn Fowler
Centers for Disease Control and Prevention (CDC)

The purpose of this session was to give an overview of the current U.S. perinatal cohorts and surveillance efforts regarding followup. As part of the session, the presenters gave an overview of the followup strategies and structure of the CDC- and NIH-supported cohorts, including both short- and longer-term followup data available to date. The cohorts presented included those followed through the CDC-supported Perinatal AIDS Collaborative Transmission Study (PACTS), the Pediatric AIDS Clinical Trials Group (PACTG) 076/219 Protocols Follow-up Study, the Women and Infants Transmission Study (WITS), and pediatric State HIV surveillance monitoring.

Overview: CDC's Perinatal AIDS Collaborative Transmission Study

Dr. Marc Bulterys
Centers for Disease Control and Prevention

Dr. Bulterys presented an overview of PACTS, a CDC-sponsored, multisite prospective cohort study of HIV-infected mothers and their children in four U.S. cities. The participating sites are located in New York City, Newark, Baltimore, and Atlanta. Enrollment for PACTS between 1986 and 1998 included over 2,600 mother-infant pairs. A total of 342 of the children in these pairs have been classified as HIV infected. Of these HIV-infected children, 212 are currently in followup and 90 have died.

Data collected include baseline demographics, medications received during pregnancy, procedures performed, and pertinent clinical and laboratory data. After delivery, the infants are followed at regular intervals. Enrollment of pregnant HIV-infected women ended on September 30, 1998. Followup will continue for all HIV-infected children enrolled in the cohort.

Research objectives for the study include the following:

- Determine rate and risk factors for perinatal HIV transmission;
- Evaluate the impact of interventions to reduce perinatal transmission;
- Describe the risk factors and spectrum of HIV-related clinical disease in infants of infected mothers and the impact of treatment of HIV and prophylaxis for opportunistic infections (OIs) on pediatric HIV disease progression;
- Evaluate methods of diagnosis of HIV disease among young infants; and
- Collaborate with other studies for combined analyses.

Examples of recent PACTS findings include the following:

- The risk of perinatal HIV transmission declined from 22 percent before 1992 to 11 percent in 1995 ($p < .001$) in association with increasing zidovudine (ZDV) (also known as AZT) use and changes in other risk factors;

- Several risk factors for transmission have been identified, including low CD4 count, long duration of ruptured membranes, prematurity, heterosexual behavior, high viral load, and maternal drug use; and

- Preterm delivery is associated more with intrapartum transmission, especially if membrane rupture is prolonged.

The following represent findings from the study of antiretroviral use after perinatal ZDV recommendations, for the period between July 1, 1994, and June 30, 1998:

- Completion of the recommended ZDV regimen (antenatal, intrapartum, and neonatal) increased from 48 percent to 71 percent overall.

- Nonutilization of the complete ZDV regimen is associated with the following:

  - Higher maternal CD4 count;

  - Preterm birth; and

  - Cocaine or heroin use during pregnancy.

- In 1997-98, 18 percent of women enrolled in PACTS received no antiretroviral therapy (ART) during pregnancy compared to >40 percent in 1994-95.

Preliminary findings on birth defects among infants exposed to ZDV i*n utero* include the following:

- 131 (5.0 percent) infants with birth defects out of 2,600 have been recorded in PACTS;

- 41 (4.3 percent) infants with birth defects out of 945 ZDV-exposed infants at any time during pregnancy have been recorded compared with 90 (5.4 percent) infants with birth defects out of 1,655 ZDV-unexposed infants; and

- 9 (3.2 percent) infants with birth defects out of 283 ZDV-exposed infants during the first trimester have been recorded.

The following table illustrates the nature of the birth defects observed in some infants exposed to ZDV *in utero* during the PACTS study, 1986-1998.

Table 1

Birth Defects in Infants Exposed to ZDV *In Utero*, 1986-1998			
Category	**Any ZDV**	**1st Trimester ZDV**	**All Infants**
Multiple Defects	3	1	20
Brain/Nervous System	4	0	11
Face and Neck	3	1	3
Heart and Circulatory	9	3	38
Orofacial Clefts	2	0	4
Genital and Urinary	5	2	12
Musculoskeletal	7	1	22
Integument	5	0	13
Chromosomal	0	0	1
All Other	3	1	7
Infants with Birth Defect	41	9	131
Prevalence at Birth	4.3%	3.2%	5.0%

For this observational cohort of PACTS, Dr. Bulterys reviewed the strengths and weaknesses of the detection of potential toxicities following perinatal exposure to antiretrovirals. The following is an outline of the observed strengths and limitations.

STRENGTHS

- Large population-based cohort of ZDV-exposed infants;
- Detailed exposure information collected prospectively; and
- Continued followup of HIV-infected children.

LIMITATIONS

- ART groups may not be comparable since ART use was not randomly assigned;
- Followup of HIV-uninfected children is terminated at 2 years of age;
- Small number of infants exposed *in utero* to combination antiretroviral therapy, with or without protease inhibitors; and
- Analyses restricted to live births.

The following is a project related to the PACTS project. This is a study entitled “Mother-Infant Rapid Intervention at Delivery” (MIRIAD), which has a projected start date of Spring 1999. It may contribute to the evaluation of ARV exposure effects.

The MIRIAD project aims to evaluate the following:

1. Innovative approaches for a 24-hour counseling and voluntary rapid HIV testing program among women in labor presenting with unknown HIV serostatus;

2. The feasibility of obtaining informed consent during labor (or, if not feasible, soon after birth);

3. Reasons for lack of prenatal care among these women;

4. The rapid implementation and assessment of antiretroviral therapy—monotherapy or more intensive regimens—given at labor and delivery and/or to the neonate;

5. Adherence to neonatal therapy; and

6. Subsequent receipt of antiretroviral treatment and other services for women identified as HIV infected.

ACTG 076 and ACTG 219

Ms. Mary Culnane
National Institute of Allergy and Infectious Diseases, NIH

Ms. Culnane summarized a recent publication of findings from the PACTG studies. This article is referenced below.

Culnane M, Fowler M, Lee S, McSherry G, Brady M, O'Donnel K, Mofenson L, Gortmaker S, Shapiro D, Scott G, Jiminez E, Moore E, Diaz C, Flynn P, Cunningham B, Oleske J. Lack of Long-term Effects of *In Utero* Exposure to Zidovudine Among Uninfected Children Born to HIV-Infected Women. *JAMA*. 1999; 281(2):151-157.

This is a prospective cohort study based on data collected during ACTG Protocol 076, a perinatal HIV prevention trial of ZDV, and Protocol 219, a long-term observational protocol. The objective of these analyses is to evaluate the long-term effects of *in utero* exposure to ZDV versus placebo among a randomized cohort of uninfected children.

Two hundred thirty-four uninfected children born to 230 HIV-infected women were enrolled in ACTG 076 and were followed up through February 28, 1997, in ACTG 219 (122 in the ZDV group and 112 in the placebo group).

The main outcome measures included the following: physical growth, immunologic parameters, cognitive/developmental function, and occurrence of neoplasms. Mortality data were assessed every 6 months for children younger than 24 months and yearly thereafter or as clinically indicated. Baseline echocardiogram and funduscopic evaluations were collected before 36 months of age.

The median age of children at time of last followup visit was 4.2 years (range: 3.2-5.6 years). There were no significant differences between children exposed to ZDV and those who received placebo in terms of sequential data on lymphocyte subsets; weight, height, and head circumference z scores; and cognitive/developmental function. No deaths or malignancies occurred. Two children (both exposed to ZDV) are being followed up for abnormal, unexplained ophthalmic findings. One child exposed to ZDV had a mild cardiomyopathy on echocardiogram at the age of 48 months; the child is clinically asymptomatic.

In summary, no adverse effects were observed in these HIV-uninfected children with *in utero* and neonatal exposure to ZDV followed up for as long as 5.6 years. Continued prospective evaluations of children born to HIV-infected women who are exposed to antiretroviral or immunotherapeutic agents are critical to assess the long-term safety of interventions to prevent perinatal HIV transmission.

The Women and Infants Transmission Study (WITS) and Combination Antiretroviral Data

Dr. Ruth Tuomala
Brigham and Women's Hospital

Dr. Tuomala described the WITS observational cohort study. She also described collaborative efforts using data from PACTS, WITS, and ACTG (076/219) to evaluate the risk of preterm delivery for women receiving monotherapy versus combination therapy with and without protease inhibitors. These data will be published shortly. In addition, another recent article summarizing followup from the WITS and ACTG studies on lack of tumors in perinatally AZT-exposed children highlights how these cohorts could be used to evaluate potential toxicities of ARV drug exposure.

Hanson C, Antonelli T, Sperling R, Oleske J, Cooper E, Culnane M, Fowler M, Kalish L, Lee S, McSherry G, Mofenson L, Shapiro D. Lack of Tumors in Infants With Perinatal HIV-1 Exposure and Fetal/Neonatal Exposure to Zidovudine. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*. 1999; 20(5):463-467.

ZDV therapy during pregnancy and to the neonate was shown to reduce perinatal HIV transmission by nearly 70 percent in ACTG Protocol 076. ZDV has been reported as positive in several *in vitro* carcinogenicity screening tests. Investigators evaluated the short-term risk for tumors in 727 children with known ZDV exposure enrolled into ACTG 076/219 and the WITS. ARV exposure (antepartum) occurred in 97 percent and 99 percent of infants in ACTG 076/219 and WITS, respectively. Median followup was 38.3 months with 366.9 person years of followup for ACTG 076/219; median followup was 14.5 months with 743.7 person years of followup for WITS. No tumors of any nature were observed; relative risk was zero (95 percent confidence interval [CI], 0-17.6). These data are reassuring regarding the short-term lack of tumors for ZDV-exposed infants observed to date. Longitudinal, standardized followup for infants with *in utero* antiretroviral exposure is necessary to assess potential long-term carcinogenicity.

Pediatric HIV/AIDS Surveillance

Dr. Mary Lou Lindegren
Centers for Disease Control and Prevention

Dr. Lindegren presented an overview of perinatal HIV/AIDS surveillance in the United States. She highlighted several aspects of perinatal surveillance, including the evaluation of current perinatal prevention efforts, the implementation of various recommendations on perinatal prevention, and the feasibility of using surveillance data to evaluate potential toxicities associated with maternal antiretroviral use.

Dr. Lindegren defined HIV/AIDS surveillance as the ongoing and systematic collection, analysis, and dissemination of population-based information on HIV infection, morbidity, and mortality. She stated that surveillance data provide the means for both monitoring the HIV epidemic in various populations and evaluating and implementing prevention services in those populations.

Surveillance data are collected either actively or passively. Passive reporting is the notification of HIV cases by health care practitioners to the proper agency based on legal regulations. Because reports made passively often lack important information, local and State health departments obtain further data through active surveillance, which is achieved through review of medical records and direct contact with health care practitioners.

Population-based HIV/AIDS surveillance, which has been conducted since 1981, has successfully served as a standardized means by which to monitor HIV infection and AIDS incidence. As AIDS surveillance underestimates the resources needed for addressing the increasing populations of HIV-exposed and HIV-infected children, population-based perinatal HIV surveillance— including perinatal HIV exposure with monitoring of HIV serostatus, AIDS, and death— provides a more timely and complete monitoring of the perinatal HIV epidemic. Perinatal HIV exposure and infection surveillance can permit us to more accurately assess resources needed for prevention, care, and social services; target and evaluate the effectiveness of perinatal prevention programs, such as the use of ZDV and other ARV therapies in pregnancy; and evaluate the impact of other public health recommendations (e.g., diagnosis, treatment, and prophylaxis guidelines). These data also can be used to facilitate the evaluation of the impact of *in utero* exposure to ARV therapy received for perinatal prevention and for treatment of mothers during gestation.

Perinatal HIV/AIDS surveillance will be used to respond to the reauthorized Ryan White CARE Act of 1996, which stipulates that CDC must develop and implement a system for States to determine annual rates of perinatally acquired AIDS (or use HIV data) and to determine causes of perinatal transmission. Perinatal HIV/AIDS surveillance also was the basis for the recent Institute of Medicine report on perinatal HIV testing.

All States currently conduct name-based AIDS surveillance, and a total of 32 States conduct name-based HIV surveillance. Three States collect information solely on children. New York will soon implement named HIV surveillance, but it also currently has a newborn HIV screening program. States without HIV surveillance are currently developing plans to implement such surveillance in order to monitor the HIV epidemic in the era of highly active antiretroviral therapy (HAART).

States with surveillance enable a timely and complete assessment of the implementation of perinatal prevention strategies and the impact on transmission rates. Surveillance entails the monitoring of children born to HIV-infected mothers, as well as followup to identify HIV infection and subsequent AIDS status. Specific data collected include information on demographics; OIs; HIV diagnostic and immunologic tests; timing of maternal HIV testing; maternal antiretroviral ZDV use during pregnancy (including week started, labor/delivery, other antiretrovirals received during pregnancy); and neonatal ZDV use, antiretroviral treatment, and prophylaxis for *Pneumocystis carinii* pneumonia. Data also include birth history information such as receipt or lack of prenatal care, prematurity, birth defects, birth weight, and type of delivery.

Because confidentiality of HIV/AIDS surveillance data is imperative, CDC requires that surveillance data be held by State and local health departments in physically secure environments with access limited to authorized health department officials. Moreover, CDC does not collect names and other personal identifiers of HIV-infected persons or those with AIDS from State and local health departments.

Current security and confidentiality laws stringently protect HIV and AIDS surveillance records maintained by health departments. A review of confidentiality laws and regulations by the Georgetown/Johns Hopkins Program on Law and Public Health found that "the strictest and most comprehensive protections of health data apply to government-held information, specifically to HIV-related information held by state health departments." CDC and the Council of State and Territorial Epidemiologists (CSTE) are currently collaborating with the aforementioned program to develop model legislation so the States can provide even stronger and more uniform protections to sensitive HIV and AIDS surveillance data. In addition, according to Federal law, no CDC HIV or AIDS surveillance data that could identify an individual, including individuals less than 18 months of age who were exposed to HIV perinatally, may be released for non-public health purposes. Disclosure of such information to the public, litigants, or non-health agencies of the Federal, State, or local governments is prohibited.

Dr. Lindegren then described the perinatal HIV epidemic in the United States with population-based surveillance data, highlighting its usefulness. Perinatal transmission of HIV accounts for virtually all new HIV infections in children. Data from AIDS surveillance and the survey estimated that approximately 16,000 HIV-infected children were born through 1995 in the United States. Through June 1998, over 7,500 perinatally acquired AIDS cases have been reported in the United States; 73 percent were diagnosed in seven States (New York, Florida, New Jersey, California, Texas, Maryland, and Pennsylvania) and Puerto Rico.

The HIV/AIDS epidemic in women is concentrated in the Northeast and in the South. While the highest rates were first observed in the Northeast, during the past 5 years the greatest increase in rates has been in the South.

African American and Hispanic women are disproportionately affected by the HIV epidemic. Over time, the number of cases among women attributable to injecting drug use has declined, while the proportion attributable to heterosexual contact has increased. There are an estimated 125,000 HIV-infected women living in the United States, of whom approximately 80 percent are of childbearing age.

The anonymous survey of childbearing women conducted in 44 States in the United States estimated the number of HIV-infected women delivering liveborn infants from 1989 to 1995 to be approximately 6,000 to 7,000 annually. Seroprevalence rates by State are similar to the geographic distribution of AIDS incidence rates in women and children, with the highest rates in the Northeast and South.

Trends in Survey of Childbearing Women (SCBW) AIDS surveillance and seroprevalence surveys increased during the 1980s, then HIV seroprevalence among childbearing women stabilized from 1989 to 1995. These trends varied by region, with the Northeast experiencing high overall seroprevalence rates but a decline after 1989 (4.1 to 3.2), and the South experiencing increasing, then stable rates (1.6-1.9). The reasons for the stabilization observed may be the result of changing reproductive decisions, stable HIV incidence among women of childbearing age, older women aging out of their childbearing years, and/or older HIV-infected women with reduced fertility due to advanced HIV disease. This estimate was extended—based upon the estimated number of women living with HIV, HIV/AIDS surveillance data, national natality data, and an estimate of incident infections in women per year—and it was estimated that the number of births to HIV-infected women from 1996 to 2005 will be approximately 60,000 to 70,000. Most of these children will be exposed to antiretroviral therapy.

Population-based data reported from 29 HIV-reporting States for over 5,000 perinatally exposed and infected children born from 1993 through 1997 whose mothers were diagnosed with HIV before or at birth highlight the increasing percentage of HIV-infected mother-infant pairs who were prescribed any of the prenatal, intrapartum, or neonatal components of the recommended ZDV regimen. The percentage of children receiving this regimen increased from 35 percent of children born in 1994 to 87 percent of children born in 1997. These data reflect rapid implementation of recommended ZDV therapy by health care providers and use of ZDV by HIV-infected mothers.

Data from the same HIV-reporting States demonstrate that the percentage of mothers diagnosed with HIV infection before or at their children's births who received prenatal ZDV increased from 28 percent in 1994 to over 70 percent in 1997. Approximately 82 percent of children born in 1997 received neonatal ZDV. Additionally, approximately 35 percent in 1998 received other antiretroviral therapy during pregnancy.

ZDV has had a profound impact on the proportion of HIV-infected children. Surveillance data are instrumental in monitoring the impact of ZDV on perinatal HIV transmission.

The implementation of perinatal prevention recommendations has been temporally associated with a substantial decline in perinatally acquired AIDS in the United States. Data indicating the number of perinatally acquired AIDS cases reported in the United States through September 1998 by quarter year of diagnosis (adjusted for reporting delay) indicate that such cases rose rapidly in the 1980s and early 1990s; peaked in 1992; and then declined 66 percent from 1993 to a new low in 1997. Declines were greatest since publication of the 1994 U.S. Public Health Service (PHS) ZDV guidelines. Declines were seen in all regions, in rural and metropolitan areas, and all racial/ethnic groups. Declines were greatest among children diagnosed in the first year of life, which would reflect efforts to reduce perinatal HIV transmission.

To further assess the implementation of perinatal prevention guidelines, identify barriers to continued reduction of perinatal transmission, and ascertain more complete HIV and ZDV exposure information, four States that conduct surveillance for HIV and AIDS (New Jersey, Louisiana, Michigan, and South Carolina) enhanced routine surveillance activities to conduct a population-based evaluation. The objectives of these efforts were to determine the proportion of diagnosed women and newborns who received ZDV prenatally, intrapartum, and neonatally; identify and characterize populations and settings where prenatal ZDV is less utilized; and determine perinatal transmission rates.

Enhanced ascertainment of mother-infant pairs included annual matching of HIV/AIDS registries to birth registries to identify all infants born to women who had been reported with HIV/AIDS, active case finding at pediatric and obstetrics sites, and followup of HIV-seropositive women pregnant at the time of the report. Ascertainment of mother-infant pairs based on these methods was comparable to the 1994 SCBW estimate of births to HIV-seropositive women, which was well over 85 percent in these States. Data about HIV testing, ZDV receipt, and prenatal care were collected from medical records for both the mother and the infant. The records used included maternal HIV clinic, prenatal clinic, and labor/delivery records as well as pediatric clinic records.

Data from this study indicate that the proportion of pregnant women in whom HIV infection was diagnosed before delivery increased from 68 percent in 1993 to 81 percent in 1996. Among these women, 52 percent had a positive HIV test before the index pregnancy and 48 percent during the index pregnancy. From 1993 to 1996, the proportion offered prenatal ZDV increased from 27 percent to 85 percent, the proportion offered intrapartum ZDV increased from 5 percent to 75 percent, and the proportion offered neonatal ZDV increased from 5 percent to 76 percent. Less than 5 percent of women refused ZDV. Of women whose HIV infection was diagnosed before delivery, 14 percent had no prenatal care.

Efforts over time supporting pediatric HIV surveillance, including perinatal exposure surveillance, have been made by the CDC, the Council of Territorial Epidemiologists, and the American Academy of Pediatrics. Increasing numbers of HIV-infected pregnant women will receive ZDV and other antiretroviral therapy during pregnancy. It was estimated that 60,000 to 70,000 perinatally exposed children will be born over the next decade, most of whom will be exposed to antiretrovirals and likely uninfected with HIV. Population-based HIV surveillance data also could facilitate the evaluation of potential toxicities of perinatal antiretroviral agents through matching of population-based registries with outcomes of concern, such as birth defects and cancer.

The United States is moving toward national HIV surveillance. Thirty-two States have perinatal HIV surveillance, with New York beginning this year. These 33 States represent 71 percent of HIV-exposed births. Of these 33 States, 13 have statewide operational birth defects surveillance, 5 have Surveillance, Epidemiology, and End Results (SEER) registries, and all participate in population-based cancer surveillance. New Jersey has piloted a program to match its HIV surveillance and birth defects registries to evaluate the incidence of birth defects among perinatally exposed children who received antiretrovirals and compare it to the incidence among those who did not receive anti-HIV drugs. Later presentations from New Jersey, Michigan, and New York State Health Departments highlight these efforts and the potential contributions HIV perinatal exposure surveillance could make to the evaluation of potential adverse events associated with perinatal antiretroviral use.

Moderator Conclusions

These presentations demonstrate that a number of different perinatal cohorts supported by NIH and CDC are in place that can provide longitudinal clinical and laboratory data regarding possible late effects of perinatal exposure to antiretrovirals and other interventions. The value of collecting these data is already evident in showing normal growth, cognitive development, and immune function through the preschool years of life. The lack of tumors and of increase in rates of birth defects also is reassuring. However, the need for long-term followup into adulthood is emphasized. In addition, the limited numbers of perinatally exposed children followed in the cohorts relative to the approximately 6,000 to 7,000 infants per year or 60,000 to 70,000 children over the next decade born to HIV-infected women who will be potentially exposed perinatally to antiretrovirals highlight the need to develop and support national surveillance approaches that will allow monitoring for possible late toxicities.

SESSION 4: SHORT-TERM SURVEILLANCE FOR BIRTH DEFECTS

Moderator: Dr. Larry Edmonds
Centers for Disease Control and Prevention

Overview of Data Sources for Birth Defect Surveillance

Dr. Larry Edmonds
Centers for Disease Control and Prevention

Major birth defects are a leading cause of infant mortality and an important public health problem. They affect 120,000 to 160,000 (3 to 4 percent) newborns each year and are responsible for 30 percent of admissions to pediatric hospitals. The 15 most significant birth defects constitute an annual cost of $8 billion. Yet, with the proper action, some causes are entirely preventable. Additional adverse reproductive health outcomes of the 3.9 million births each year in the United States also are of significance, including low birth weight (7.3 percent), very low birth weight (1.3 percent), preterm births (11 percent), infant deaths (8 percent), and developmental disabilities such as mental retardation (1 percent), cerebral palsy (0.2 percent), and visual impairment (0.06 percent).

Annually, among approximately 6,000 HIV-exposed births per year, we would expect 180-240 infants with major malformations (3 to 4 percent), 438 (7.3 percent) with low birth weight, 78 (1.3 percent) with very low birth weight, and 660 preterm births (11 percent). Estimates of adverse reproductive outcomes occurring annually among an estimated 1,458 HIV-exposed infants in New York include 58 with major birth defects (including 1 to 2 neural tube defects and 1 to 2 orofacial clefts) and with developmental disabilities (14 with mental retardation and 3 with cerebral palsy). Similarly, in the 395 HIV-exposed infants per year in New Jersey, we would expect 16 major malformations, e.g., 0-1 infants would have either neural tube defects or orofacial clefts, 4 would have mental retardation, and 0-1 would have cerebral palsy.

The best resources for approaching surveillance of populations exposed to potential toxicants include astute clinicians, exposed cohort studies, case-control surveillance, adverse drug reaction reports, drug registries, and population-based surveillance recommendations, specifically those that call for linking HIV-exposed surveillance registries that include antiretroviral exposure data to Birth Defects Surveillance registries.

Birth defect surveillance data are obtained from multiple sources: vital records (birth, infant death, and fetal death certificates), hospital records (discharge summaries, disease indexes, nursery logs, neonatal intensive care unit logs, and specialty clinic records), administrative databases (Medicaid, State hospital discharge, and health maintenance organization [HMO] databases), special data sources (special health care need programs and specialty clinics, e.g., genetic clinics), and prenatal diagnosis center and clinical examination records (from the Collaborative Perinatal Project [CPP], hospital-based surveillance, and special studies). The quality of data varies by data source. For example, birth certificates are considered to have a predictive value positive of 76 percent but a sensitivity of only 28 percent, while hospital discharge data have a predictive value positive of 85 to 95 percent and a much higher sensitivity (70 to 90 percent). Both inpatient and outpatient charts are important to include, as some defects are more likely to be picked up early from

inpatient records, and some defects are more likely to be diagnosed later in infancy in the outpatient records.

Different case ascertainment methods exist for identifying infants with birth defects. In some geographic areas, such as those included in the Collaborative Perinatal Project, attempts are being made to examine every baby born. Active surveillance is conducted in a number of areas (e.g., Iowa, Hawaii, and metropolitan Atlanta) by reviewing medical records, including hospital data from nurseries, neonatal intensive care units, specialty clinics, laboratories, and screening programs. Hospital discharge summaries or disease indexes can identify records, and some areas use existing hospital discharge data and outpatient data (Connecticut, National Birth Defects Monitoring Program, and the Healthcare Cost and Utilization Project [HCUP]). New York and New Jersey have implemented legislative mandates for hospital or physician reporting. Some areas maintain linkage of multiple data sources, and others link vital statistics—births, deaths, and fetal deaths. Finally, other data sources can be used, such as prenatal diagnosis and physician records and those maintained by genetic clinics, Medicaid, special health care needs programs, and special surveys. Hospital discharge data and multiple sources provided the greatest yield for cases based on a study in North Carolina, where 68 percent of infants with birth defects were ascertained through hospital discharge data compared to 4.3 percent from birth certificates alone and 20 percent from multiple sources. Rates of major birth defects also vary by source of data; for example, the overall major birth defect rate using birth certificates is only 1.5 percent compared to a rate of 4.3 to 7.1 percent using newborn hospital discharge data or 3.4 percent for mandatory hospital reporting.

Currently, Statewide birth defects surveillance systems are operational in 30 States, which cover approximately 58 percent of the annual U.S. births, and are newly implemented or planned in 13 additional States (Figure 1). Birth defects surveillance case definition is specific and includes specific definitions of each major and minor malformation, excluded conditions, and other birth defects and biochemical and genetic diseases; it also includes parameters related to gestational age, birth weight criteria, and the infants' age as well as prenatal diagnoses.

Additionally, eight Centers of Excellence for birth defect research and surveillance have been funded since 1996 (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, and Texas). All of these areas also participate in the National Birth Defects Prevention Study, which includes a large case-control study of birth defects risk factors. New Jersey's proposed research activity is to study the effect of perinatal ARV drug exposure on newborns by linking its HIV surveillance registry to its birth defects registry.

In summary, birth defects are an important public health concern. The impact of antiretroviral drugs is unknown and difficult to evaluate due to small numbers of annual births. Standardized Review and Classification for exposure and outcome are needed. A combined approach may best address these concerns, including the following activities: exposed cohort studies, population-based surveillance (linking exposure and outcome registries), central drug registries, and case-control studies.

Figure 1


Current State Activities in Birth Defects Surveillance
Operational
Planning/ Newly Implemented
Other
Jan 1999
CDC

Antiretroviral Drug Registries for Birth Defects

Dr. Alice White
Glaxo Wellcome, Inc.

The Antiretroviral Pregnancy Registry (APR) is an international registry that was established in 1989 and currently is sponsored by Glaxo Wellcome, Hoffman-LaRoche, Bristol-Myers Squibb, Agouron Pharmaceuticals, Abbott Laboratories, Dupont Pharmaceuticals, and Boehringer Ingelheim Pharmaceuticals. The objectives of APR are to be able to provide an early warning signal of major teratogenicity associated with prenatal exposure to licensed antiretrovirals and to estimate the risk of major birth defects and compare it to the risk for the general population. The registry is international in scope, collects data voluntarily reported by health care providers of prenatal exposure in all trimesters, and is able to capture all the information in one place. This registry is overseen by an advisory committee representing CDC, NIH, obstetrics/gynecology practitioners, public health departments, and other sponsors. Any cases of women exposed prenatally for any reason are referred to the registry by the treating health care provider. Outside of North America, reports can be made directly to the registry or through a manufacturer operating company. These data supplement animal toxicology and clinical studies. Baseline maternal data are collected including medical chart number, demographics, treatment history (dose, duration, and indication), and health care provider contact information. At the estimated delivery date, a followup form is sent to the health care provider, and data are collected on medication history, pregnancy outcome (live infant, spontaneous abortion, induced abortion, stillbirth), and birth defects. For children with birth defects, targeted followup includes an additional questionnaire to assess maternal history and maternal exposures and address questions specific to the defect based on CDC teratology review. Data are sent to the manufacturers for expedited reporting. The information in the registry is confidential; any identifying information provided to the registry is deleted at closure.

The data are reviewed semiannually by the advisory committee, with separate analyses of prospective and retrospective reports. Data analysis includes evaluating all birth defects and analyzing defects for any evidence of patterns. CDC estimates of “expected” risk are compared to the estimate of risk from the registry. Finally, an advisory committee consensus statement is published with data in an interim report. The challenge is to define the exposures. The role of the advisory committee is to review and approve study methods, conduct case investigation of birth defects, review data and arrive at a consensus statement, refer exposures, and disseminate the information.

This advisory committee oversight is considered one of the strengths of the registry. Additionally, the registry provides a method to detect a signal when there are no *a priori* hypothesis and numerator/denominator values for risk estimates. The broad-based participation in the registry is another advantage to the program. However, because of a lack of awareness of the program and its voluntary format, underreporting poses limitations on the registry. The registry also is prone to potential selection biases, short-term followup only, and loss to followup (20 to 25 percent). Issues of informed consent with voluntary registry pose further challenges. Examples of recent data are shown in Tables 1 and 2.

Table 1

Birth Outcomes by Earliest Trimester of Exposure

Overall Drug Regimens

Prospective Data Through 31 July 1998

Trimester of Earliest Exposure	Outcomes with Birth Defects	Live Births (no defects)	Spontaneous Pregnancy Loss (no defects)	Induced Abortion (no defects)	Total
First	5	219	14	52	290
Second and Third	12	338	7	0	357
Total	17	557	21	52	647

Table 2

Birth Defects Reported by Type of Defect

Overall Drug Regimens and All Trimesters

Prospective Data as of 31 July 1998

Number of Outcomes with >= 1 Defect	17
Type of Defect[a]	
Musculoskeletal	6
Cardiovascular	4
Limb Defects[b]	3
Chromosomal	2
Cranium	2
Eye Defects	2
Other[c]	10

[a]An outcome may have more than one defect

[b]Includes 1 limb deficiency defect

[c]Other includes: respiratory (2); Urinary tract (2); Ear (1); Oral cleft (1); Integument (1); Intestinal (1); Not specified (2)

Overview of Other Registries and Approaches

Dr. Allen A. Mitchell
Boston University School of Public Health

Dr. Mitchell began his talk by separating the sources of information on human teratogenesis into premarketing and postmarketing. Premarketing includes *in vitro* and animal studies as well as human clinical trials. He noted that human trials could provide rather small samples and could not be considered completely representative of the "real world." Postmarketing data collection involves case reports (both published and unpublished), experimental studies such as clinical trials, and nonexperimental or epidemiologic studies including cohort and case-control studies. Cohort studies are broad-based and are able to study a wide range of exposures (e.g., U.S. CPP); they also can be focused studies on specific exposure (e.g., registries sponsored by manufacturers or teratogen information services). Case-control studies also are broad-based and can address a wide range of defects (e.g., CDC Centers for Excellence in Birth Defects Research and Prevention; SEU Birth Defects Study); they also can be focused on specific defects (e.g., oral clefts and others too numerous to count). The different strengths between the two types of epidemiologic studies are that cohort studies evaluate rare exposure, minimize bias in ascertaining exposure, and measure risk directly, while case-control studies evaluate rare diseases, minimize bias in ascertaining diseases, and require minimum cost in time and dollars. The limitations of these studies are that cohort studies can have problems with dropout rates, and challenges for case-control studies lie in the choice of appropriate controls.

Dr. Mitchell also focused on special considerations in the evaluation of antiretrovirals and birth defects. He provided examples of some drugs known to cause birth defects in humans (Table 1). He explained that the fallacy of "class action" teratogenesis is that members of a given drug class do not necessarily have the same teratogenic (or nonteratogenic) activity. With this in mind, the question of *exposure* becomes: can all antiretrovirals be evaluated as a class or must the risk of each antiretroviral and each combination regimen be evaluated separately?

Table 1

Some Drugs Known to Cause Birth Defects in Humans

Drug	Effect
Thalidomide	Phocomelia
Synthetic progestagens	Masculinization of female genitalia
Diethylstilbestrol	Vaginal Cancer
Folic acid antagonists (e.g., methotrexate)	Craniofacial anomalies, growth retardation
Alkylating agents (e.g., chlorambucil)	Miscellaneous serious effects
Tetracycline	Dental enamel staining, bone effects
Warfarin	Bone and cartilage defects
Lithium	Cardiac defect
Valproate	Neural tube defects
Isotretinoin (Accutane)	Facial, CNS, cardiac defects

Similarly, should the *outcomes* of concern be specific birth defects or birth defects overall? When it comes to specific birth defects, every outcome is rare. For example, rates range from 7 per 10,000 births for Down's syndrome to 0.8 per 10,000 for transposition of the great vessels.

The situation is further complicated by potential confounding factors related to HIV. HIV-related conditions exist in a complex milieu of covariates that can confound antiretroviral/birth defect assessments. Along with HIV infection itself, drugs other than antiretrovirals (prescribed, illicit, over the counter), nontraditional treatments, diets, and health behaviors can be variables that complicate defect assessments. Final questions that must be addressed in considering antiretroviral/birth defects are those of *power*: (1) How small a risk can/should be detected? and (2) How large a risk can acceptably go undetected?

Some examples of power calculations for risk as common as 1 per 1,000 and 1 per 10,000 are found in Tables 2 and 3, respectively.

Dr. Mitchell reached the tentative conclusion that a clinically meaningful assessment of the potential teratogenicity of specific antiretrovirals or specific combination regimens presents a daunting challenge.

Table 2

Implications for statistical power:

For a relatively "common defect" such as oral cleft, which affects 1 per 1000 births:

To identify a risk of at least	Need to follow: exposed	not exposed	Total
3 fold	7500	15,000	22,500
5 fold	2800	5600	8400
10 fold	1000	2000	3000

Table 3

Implications for statistical power:

For a defect affecting 1 per 10,000 births:

To identify a risk of at least	Need to follow: exposed	not exposed	Total
3 fold	75,000	150,000	225,000
5 fold	28,000	56,000	84,000
10 fold	10,000	20,000	30,000

The Role of the Clinician for Identification of Potential Syndromes: Historical Perspective of Fetal Alcohol Syndrome

Dr. Kenneth L. Jones
University of California, San Diego

Dr. Jones highlighted the contribution of minor malformations to the recognition of a potential syndrome. He used the example of the fetal alcohol syndrome, which consists of a pattern of malformations that includes both major and minor malformations. He also highlighted the California Teratogen Information Service that was established in 1979 and follows children from 1 to 4 years of age and includes an examination by a provider.

SESSION 6: EPIDEMIOLOGY AND STATISTICS

Moderator: Dr. Sandra Melnick
National Cancer Institute, NIH

Basic Epidemiologic Concepts

Dr. Guthrie S. Birkhead
New York State Department of Health

Dr. Birkhead described basic epidemiologic concepts that are important in the context of studies to address toxicities of ARV in pregnancy. Epidemiology is the study of the occurrence of diseases in human populations. *The Dictionary of Epidemiology* defines epidemiology as the study of the distribution and determinants of health-related states or events in specified populations, and application to control. In other words, it is the task of epidemiologists to determine whether exposure to Factor A causes Disease B. This challenge entails defining and measuring disease occurrence, defining and measuring exposure to disease-causing factors, and determining the relationship between the two (accounting for other factors). Disease occurrence is defined using case definitions, such as the pediatric HIV case definition and congenital malformation definitions, and using case findings through surveillance (for HIV, birth defects, or cancer) or assembling study groups at clinical sites. Exposure is defined as ZDV or other factors and has to be measured using verbal history, medical chart review, or laboratory measurement. The goal of the study is to determine the association between exposure and disease, accounting for other factors. A measure of this association includes relative risk (RR), or the incidence of disease in persons exposed to the factor of interest divided by that in unexposed persons. An RR greater than 1 indicates an association (exposure is associated with disease), while an RR less than 1 indicates a protective effect (exposure is associated with less disease). In case-control studies, an approximation of the RR, the odds ratio, is calculated and utilized.

These studies also search for the perfect numerator and denominator to determine disease rates. Measures of disease occurrence are in the form of proportions (ratios) and rates (per unit time; "risk"). The proportion measures prevalence by taking the number of persons with a disease at a given time over the number of persons in the population at that time. The rate determines incidence or incidence density by taking the number of persons acquiring a disease during a period over the number of persons at risk and the time they are at risk.

Epidemiologic studies can be either experimental (such as clinical trials) or observational, depending on whether there is planned intervention or no intervention at all. There are two types of observational (no intervention) studies: cohort and case-control studies (see Figures 1 and 2). Cohort studies are defined by exposure status, and then disease occurrence is measured. A case-control study is retrospective; study groups are defined by disease occurrence, and then exposure is measured. Cohort studies require large numbers to study rare outcomes, and directly measure incidence and RR, but have potential bias in assessing outcome. Case-control studies, on the other hand, are more efficient in terms of numbers of subjects and time, can measure the odds ratio but not incidence, and have potential bias in assessing exposure and selection of controls.

Figure 1

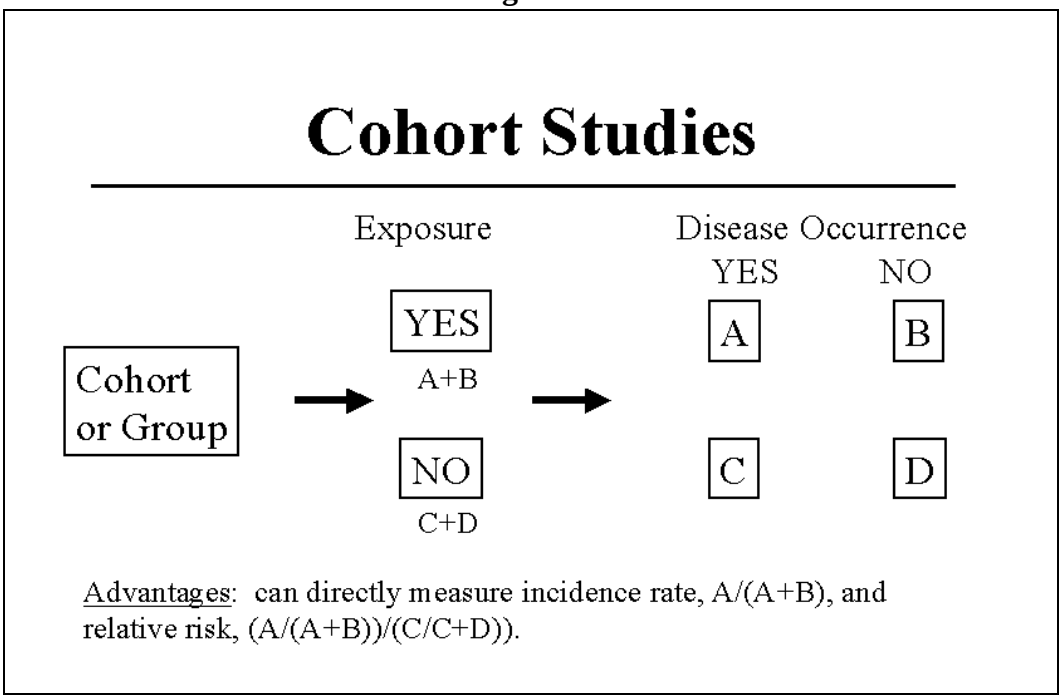
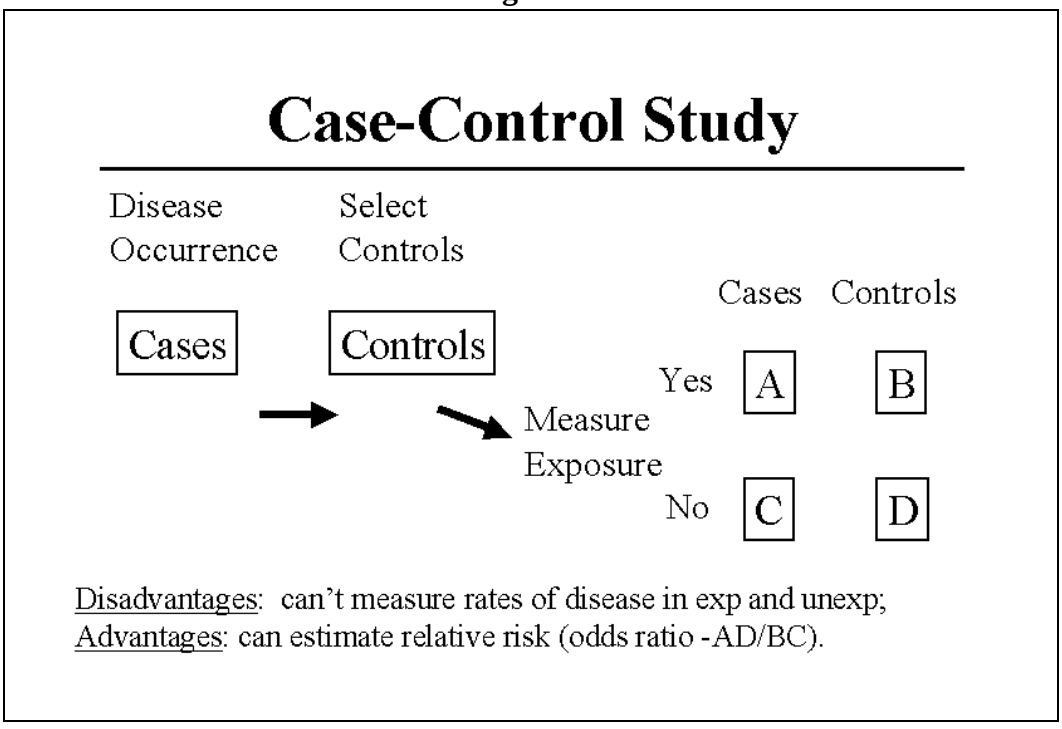


Figure 2



Dr. Birkhead then explained that the causal significance of a statistical association is dependent on the following:

- Strength of the association (relative risk)
- Specificity of the association
- Biologic gradient (dose-response)
- Temporal sequence
- Consistency of findings
- Replication of findings
- Biologic plausibility

A “web of causation” is created when a single outcome has multifactorial causes, such as environmental factors or genetic susceptibility. Similarly, a single cause may have multiple outcomes, such as cancer (multiple sites, latencies, etc.) or birth defects. A statistical association may be causal or noncausal. A noncausal statistical association could be explained by random variation, by bias (selection of groups, misclassification, etc.), or when disease and exposure are both related to another causal factor (confounding). Lack of a statistical association can be explained by insufficient statistical power, biases (selection of groups, misclassification, etc.), unequal distribution in study groups of another causal factor (confounding), or the absence of causation (exposure does not cause disease).

Basic Principles for Surveillance Systems and Studies

Dr. Philip Rhodes
Division of HIV/AIDS – Surveillance and Epidemiology
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Dr. Rhodes outlined issues pertaining to statistical considerations of evaluating potential toxicities of ARV, highlighting the contributions of surveillance. He defined surveillance using several quotes. In 1988, Thacker said, "Public health surveillance is the ongoing systematic collection, analysis, and interpretation of outcome-specific data for use in the planning of public health practice."[1] In 1971, Langmuir discussed the tendency of epidemiologists to equate surveillance with most of epidemiology, including epidemiologic investigations and research.[2] In 1994, Thacker added, "Surveillance data should be used to identify research and service needs, which in turn, help to define training needs….However, surveillance does not encompass epidemiologic research….Thus, the boundary of surveillance practice excludes actual research and implementation of delivery programs."[3]

Dr. Rhodes continued to define surveillance by listing its multifarious uses, according to Thacker.[3] The uses of surveillance include the following: quantitative estimate of the magnitude of a health problem, portrayal of the natural history of an epidemic, detection of epidemics, documentation of the distribution and spread of a health event, facilitation of epidemiologic and laboratory research, testing of hypotheses, evaluation of control and prevention measures, monitoring of changes in infectious agents, monitoring of isolation activities, detection of changes in health practice, and planning.

In particular, HIV/AIDS surveillance is the ongoing and systematic collection, analysis, and dissemination of population-based information on HIV infection, morbidity (such as AIDS), and mortality. HIV/AIDS surveillance data are used to estimate the burden of HIV infection and severe disease in the population; monitor trends in the HIV epidemic and identify populations at risk; target HIV prevention interventions and evaluate their effectiveness; allocate funds for health and social services; and facilitate access to health, social, and prevention services.

Elements of surveillance systems include case definitions, data collection, standardization, active versus passive systems, limited surveillance systems, field testing, data analysis, interpretation and dissemination, and evaluation.[4] Case definitions can be self-reports or physician diagnoses,

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[1]Thacker S and Berkleman R. Public Health Surveillance in the United States. *Epidemiologic Reviews* 1988;10:164-190.

[2]Langmuir A. Evolution of the Concept of Surveillance in the United States. *Proc R Soc Med* 1971;64:681-689.

[3]Thacker S. Historical Development. *In* Teutsch and Churchill (Eds.), *Principles and Practice of Public Health Surveillance* 1994;3-17.

[4]Teutsch S. Considerations in Planning a Surveillance System. *In* Teutsch and Churchill (Eds.), *Principles and Practice of Public Health Surveillance* 1994;18-28.

laboratory tests, and clinical findings. Each case is then categorized as possible, probable, or definite, and the case is described by severity and subtypes. There is usually a tradeoff between the sensitivity and the specificity of the case definition. *Sensitivity* refers to what proportion of true cases are found, while *specificity* refers to what proportion of diagnosed cases are true cases.

Dr. Rhodes highlighted these issues using the CDC Case Definition and Classification of Measles as an example. By the clinical case definition, an illness is characterized by all of the following: a generalized rash lasting greater than or equal to 3 days, a temperature greater than or equal to 101.0 ºF (greater than or equal to 38.3 ºC), and cough, coryza, or conjunctivitis. The laboratory criteria for diagnosis include a positive serologic test for measles immunoglobulin M antibody, or a significant rise in measles antibody level by any standard serologic assay, or the isolation of measles virus from a clinical specimen. The case is classified by the following categories:

Suspected: Any febrile illness accompanied by rash.

Probable: A case that meets the clinical case definition, has noncontributory or no serologic or virologic testing, and is not epidemiologically linked to a confirmed case.

Confirmed: A case that is laboratory confirmed or that meets the clinical case definition and is epidemiologically linked to a confirmed case. A laboratory-confirmed case does not need to meet the clinical case definition.

There is a great amount of variability in the amount and detail of information that is collected by various surveillance systems. This variability reflects the tension between the desire to collect as many cases as possible and the limited resources that are available to perform data collection.

The level of case ascertainment and the amount of information collected on HIV/AIDS cases is indicative of the level of resources devoted to this system. HIV/AIDS surveillance data include demographic characteristics, risks for HIV infection, opportunistic illnesses and immunologic status, and supplemental information. HIV/AIDS surveillance data are collected in both passive and active systems. Passive reporting occurs when health care practitioners, hospitals, clinics, and laboratories report cases of HIV/AIDS to State and local health departments. Active surveillance, on the other hand, requires State and local health departments to collect information by contacting health care practitioners and reviewing medical records in hospitals and clinics.

There are many different sources of routinely collected data for surveillance:[5]

- Notifiable disease reporting systems (infectious diseases or resulting morbidity, e.g., measles, pertussis, AIDS)

- Vital statistics (birth records, death records)

- Sentinel surveillance (varicella incidence in a small group of counties)

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[5]Stroup N, Zack M, and Wharton M. Sources of Routinely Collected Data for Surveillance. *In* Teutsch and Churchill (Eds.), *Principles and Practice of Public Health Surveillance* 1994:31-85.

- Registries (cancer SEER, birth defects, exposure to antiretrovirals during pregnancy)

- Health surveys (National Health Interview Study [NHIS], National Health and Nutrition Examination Survey [NHANES], Behavioral Risk Factor Survey [BRFS])

- Administrative data collection systems (Vaccine Safety Datalink Study, hospital discharge data sets)

Dr. Rhodes then addressed the types of studies that can be performed using (a) surveillance data as a starting point or (b) only surveillance data (Table 1).

Table 1

Case-Based Surveillance Data

		Risk Factor: **Yes**	Risk Factor: **No**
Outcome	**Yes**	a	b
	No	c	d

If 'outcome' is the case definition that defines inclusion in the surveillance system, then at best we will know 'a' and 'c' (assuming that the 'risk factor' has been measured on all cases). Thus, to evaluate the association between the outcome and the risk factor we require auxiliary information about the distribution of the exposure among those without the outcome. In some instances this information may be available from other sources, e.g., suppose risk factor = gender, race/ethnicity, or proportion receiving some vaccine. If this information is not available, then some additional effort will be required in order to determine this distribution. In most cases, this will be the sample of those without the outcome. Thus, we would be conducting a case-control study.

Suppose, however, that we are interested in 'outcome' only within persons who are cases in the surveillance system. Thus, if we know the status of 'outcome' and 'risk factor' among the cases in the system we can fill in the four cells of the table. If we also know about the temporal sequence of 'outcome' and 'risk factor' (if appropriate), then we are in position to conduct a cohort study.

Dr. Rhodes proceeded to demonstrate examples of power calculations in surveillance studies (Table 2).

Table 2

Comparing Two Study Groups of Equal Size						
N = Required number in each group						
Unexp Risk.	**Exp. Risk**	**RR**	**N**	**Power**	**Unexp. Cases**	**Exp. Cases**
5/1,000	10/1,000	2	5,080	.80	25.4	50.8
5/1,000	15/1,000	3	1,750	.80	8.8	26.4
2/1,000	4/1,000	2	12,700	.80	25.4	50.8
2/1,000	6/1,000	3	4,400	.80	8.8	26.4
2/1,000	10/1,000	5	1,700	.80	3.4	17
1/1,000	3/1,000	3	8,800	.80	8.8	26.4
1/1,000	5/1,000	5	3,400	.80	3.4	17
1/1,000	9/1,000	7	450	.80	0.5	3.2
1/2,500	3/2,500	3	22,000	.80	8.8	26.4
1/2,500	5/2,500	5	8,550	.80	3.4	17
1/2,500	7/2,500	7	1,130	.80	0.5	3.2

Notes:

1. The crucial factor is the expected number of cases in the two groups.

2. For relative risks ≥ 5, the 'required' expected number of events becomes quite small. Given the possibility of misclassification in case status, one should view the sample sizes given above as minimal rather than adequate group sizes.

3. Even with 'good power,' one may not achieve confidence intervals that are of a desirable width. For example, a study with 9 unexposed and 27 exposed cases from groups of equal sizes would have an RR = 3.0 with a 95 percent CI = (1.4, 6.4). A study with 4 unexposed and 20 exposed cases from groups of equal sizes would have an RR = 5.0 with a 95 percent CI = (1.7,14.6).

Dr. Rhodes next demonstrated an example of evaluating observed cases in an exposed group to an assumed population risk (Table 3).

Table 3

Comparing An Exposed Group to An Assumed Population Risk					
Assumed Background	**Exposed Risk**	**Exp. Pop. Size**	**Min. Cases**	**RR**	***p***
1 per 1,000	1,000	1	≥4	4.0	.019
	2,000	2	≥6	3.0	.017
	5,000	5	≥10	2.0	.032
	10,000	10	≥16	1.6	.049
1 per 2,500	2,500	1	≥4	4.0	.019
	5,000	2	≥6	3.0	.017
	10,000	5	≥10	2.0	.032
	25,000	10	≥16	1.6	.049

Note: The expected number of events—background risk × population size—is the crucial factor.

Dr. Rhodes concluded by considering surveillance of birth defects in association with antiretroviral treatment. He discussed the detection of risk factors for birth defects. According to Khoury, et al., it is easier to detect a risk factor that affects two (or more) birth defects.[6] For example, consider birth defects A and B, which both occur with a probability of 1 per 1,000, but occur with a joint probability of 1 per 10,000. Since independence would imply that joint probability 1 per 1,000,000 (1 per million), there is an association between A and B (Table 4).

Table 4

Unexposed Population

		B		
		Yes	**No**	**Total**
A	**Yes**	1	9	10
	No	9	9,981	9,990
	Total	10	9,990	10,000

[6]Khoury MJ, Adams MM, Rhodes P, Erickson JD. Monitoring for Multiple Malformations in the Detection of Epidemics of Birth Defects. *Teratology* 1987 Dec;36(3):345-53.

Suppose that exposure has an effect on outcomes A and B but that most of these occur together, i.e., consider Table 5:

Table 5

Exposed Population

		B		
		Yes	**No**	**Total**
A	**Yes**	9	11	20
	No	11	9,169	9,980
	Total	20	9,980	10,000

Under either of the following scenarios it is easier to detect the effect of the exposure on the joint outcome A-B than on A or B separately.

- Observing two populations (unexposed and exposed) with 10,000 births in each with outcomes as observed in Tables 4 and 5:
  - Separate analysis: analyzing A separately yields the following analysis (odds ratio = 2.0, $p = .073$)
  - Combined analysis: analyzing A and B jointly yields the following analysis (odds ratio = 9.0, $p = .020$)

Note: Using A or B as the outcome of interest would not be an improvement since there are 31 events in the exposed population and 19 events in the unexposed (odds ratio = 1.63, $p = .092$).

- Comparing the exposed population (Table 5) to population risks equal to probabilities in the unexposed population (Table 4):
  - Separate analysis: $p = .002$
  - Combined analysis: $p < .00001$

When studying antiretroviral-birth defects associations, HIV surveillance can be used alone or in conjunction with birth defects surveillance. By itself, HIV surveillance (1) finds infants who are born to HIV-infected women, (2) collects information on prenatal exposure to ZDV (or other antiretrovirals), and (3) gathers information on birth defect outcomes for the children. However, the drawback to using only HIV surveillance is that the birth defect outcome is not very standardized and may be missing.

Using HIV surveillance with birth defects surveillance (1) finds infants who are born to HIV-infected women, (2) collects information on prenatal exposure to ZDV (or other antiretrovirals), and (3) links the systems that find those infants who have birth defects born to HIV-infected mothers. The obvious advantage of this combined surveillance is that case ascertainment and categorization are more standardized.

In summary, surveillance systems are different than epidemiologic studies. ‘Notifiable systems’ are more routine and have more longevity than planned studies but may be less standardized and gather much less information. Also, research may be conducted using surveillance data depending upon the type of question asked and the amount of information gathered by the system. Otherwise, auxiliary information will be necessary.

SESSION 7: SETTING UP REGISTRIES AND COHORTS

Moderator: Dr. Martha Rogers
Centers for Disease Control and Prevention

Confidentiality, Ethical, and Legal Issues

Dr. Zita Lazzarini
University of Connecticut Health Center

Dr. James G. Hodge
Georgetown University Law Center

Drs. Lazzarini and Hodge began by introducing the potential scope of the project, which would involve using public health data to identify infants exposed to potentially toxic ARV therapies and to do research on toxicities (matching birth and exposure data with birth defects, cancer registries, and death records). This proposed project entails expanding regularly collected public health data to include the nature and quantity of ARV therapy exposures, other medical history, and potentially up-to-date locator information. If links are established to increased risk of cancer, birth defects, other morbidity, and mortality, then the issuance of a public health alert to providers to alert them to the risk and to contact children/parents directly to warn them of the risk will be necessary.

They noted that law, ethics, and public health intersect at various points in this endeavor. They discussed the broad ethical and legal questions raised by potential ARV drug toxicity research and the particular impact that ethical concerns about individual privacy and health information privacy and antidiscrimination laws create for these types of projects.

Issues for Public Health Officials and Individual Providers

There are important ethical questions for public health officials and individual providers to address, such as: What is the public health justification for doing this at all? The *consequentialist justification* says that public health measures/surveillance are justified if their probable benefits outweigh their probable burdens. For example, the benefit of possible detection of adverse consequences of ARV therapy must be balanced against the potential burdens, such as risks to health information privacy. The *principlist justification* says that important principles may require health authorities to take steps to avoid or mitigate increased risks of harm that patients may experience from following public health recommendations. For example, public health officials have strongly encouraged testing and ARV treatment of pregnant women and infants, but to ensure nonmaleficence, public health officials (and pharmaceutical manufacturers) should take a variety of steps to uncover potential risks that those recommendations may create.

There is another ethical question: What are the ethical and legal obligations of individual practitioners? The principled obligation is much the same as in the public health justification: Providers encourage pregnant HIV-infected women to take ARV drugs, thereby creating clear benefit for some and putting others in "harm's way." As a consequence, a provider has a duty to avoid harm if possible (nonmaleficence) and mitigate any harm that might arise from complying

with clinical and public health advice. The provider has the responsibility to inform patients of the potential risks of ARV therapy as yet undefined, provide followup for the duration of the provider-patient relationship, comply with any public health provisions that promote long-term followup, and inform patients about collection of these data.

Legal Issues

Along with these ethical questions, there are legal questions that must be addressed as well. For example: *Does the law in specific States in question authorize collection and uses of the relevant data?* Other questions that must be answered include the following: (1) What data need to be collected? and (2) Is additional authorization needed, e.g., is special authorization needed in some areas in the case of retrospective coverage of births back to 1994 when ARV therapy was first used? Another issue is how parents are notified, so that this information will be collected, and informed of the positive benefits and the protection in the law to reduce burdens to the patient and protect family privacy.

Specific concerns with individual privacy of health information were also discussed. For example, they discussed how and to whom information is disclosed. Another issue discussed was the use of aggregate versus personally identifiable data. Matching with other databases will require matching with data collected for different reasons. This use of the data is justified, as it is intended to benefit public health and it may be of potential clinical benefit to the individual. However, there may be legal impediments in specific States. Nevertheless, using aggregate data alone will not be feasible because research requires accurate matching of individual records. Additional issues discussed included the sufficiency of existing laws to prevent secondary uses not aimed at detecting, preventing, and mitigating toxicities of ARV drugs. Finally, whether children and parents will be recontacted with a notice needs to be taken into consideration.

Possible conflicts may exist with family law/probate law provisions; for example, adoption laws with the new birth certificate may interfere with identification, tracking, and collection of data. The issue of foster parents' access to HIV-related information must be considered as well.

Personal liability issues for practitioners must be considered, particularly the fear about liability for toxicities that were not known at the time treatment was recommended. Means to avoid potential liability include securing informed consent for treatment with fair disclosure of potential for risk, continuing analysis of any potential risk in the context of clear benefits, and having public health officials and clinicians respond promptly to identified adverse consequences.

The Impact of State and Federal Privacy Laws on ARV Drug Toxicity Tracking Efforts

Dr. Lazzarini and Dr. Hodge defined "health information privacy" as an individual's claim to control the circumstances in which personally identifiable (versus anonymous or linkable) information is collected, used, and transmitted. "Confidentiality" involves the privacy interests arising out of a specific relationship with the person about whom information is gathered (i.e., doctor/patient relationship), and "security" refers to technological, organizational, or administrative processes designed to protect data systems from unwarranted disclosures, modification, or destruction. They noted that privacy can never be fully maintained even with

security provisions at their maximum, because no collection of information is free from authorized access.

While the Federal Constitution does not expressly provide individuals with privacy rights, the Supreme Court has recognized a limited right to health informational privacy as a liberty interest within the Fifth and Fourteenth Amendments. However, the courts regularly allow infringements on informational privacy through the administration of a flexible test, balancing the invasion of privacy against the strength of the governmental interest. Provided the Government articulates a valid societal purpose and employs reasonable security measures, courts have not interfered with traditional governmental activities of health information collection and distribution.

The Federal Government has enacted several statutes and regulations to protect privacy of health information: the Privacy Act of 1974, which requires Federal agencies to utilize fair information practices with regard to the collection, use, or dissemination of systematized records; The Freedom of Information Act of 1966 (FOIA), which requires the Federal Government to provide various information but exempts from governmental disclosure several categories of records, which include health information; and the Electronic Communications Privacy Act of 1986, which protects electronic communications during transmission or while in storage against unauthorized interceptions and improper uses, although it likely does not protect interceptions on nonencrypted information over radio frequencies. Federal regulations require privacy protections in relation to the administration of human subject research (45 CFR §§ 46.101-.404). While informed consent of subjects is the norm for research involving identifiable information, institutional review boards (IRBs) can waive some or all of the elements of informed consent.

The Health Insurance Portability and Accountability Act (HIPAA), Public Law 104-191, seeks to reduce the administrative and financial burden of health care by standardizing the electronic transmission of health-related data. The HIPAA requires the Department of Health and Human Services (DHHS) to set uniform standards for the transmission of health insurance information and includes recommendations for security measures to protect private information. The five key principles of the DHHS recommendations are as follows:

1. Boundaries—health care information should be disclosed for health purposes only, with limited exceptions;

2. Security—health information should not be distributed unless the patient authorizes it or there is a clear legal basis for doing so, and those who receive such information must safeguard it;

3. Consumer control—persons are entitled to know of and correct information in their health records and the purposes in which it is being used;

4. Accountability—those who improperly hold, distribute, or use health information should be criminally punished, especially when such actions are for monetary gain. Those individuals affected by such actions should have civil recourse; and

5. Public responsibility—privacy interests of individuals must not override national priorities of public health, medical research, human subjects research (HSR), health care fraud and abuse, and law enforcement in general.

The intent of the DHHS regulations and HIPAA itself is not to preempt all State regulation of privacy rights and health information, but rather to provide a floor for national uniformity. Only State laws that are less protective of Federal privacy rights would be preempted; laws which are more protective would survive. Finally, the current Federal Privacy Bills are Federal bills on health information privacy and genetic privacy and are circulating in Congress. Since the 1970s, more than a dozen States have adopted constitutional amendments designed to protect a variety of privacy interests, including limitations on access to personal information. Most of the State constitutional provisions protect only against breaches of privacy by government. States have enacted health information privacy protection in many forms, including laws similar to the Federal Privacy Act and FOIA. A few States have passed comprehensive medical information statutes that prohibit medical providers from disclosing identifiable health information without a patient's written consent, unless the disclosure is required or authorized by law or for purposes of research pursuant to IRB approval. States also have passed disease-specific privacy laws, including privacy laws concerning HIV infection or AIDS. State case law imposes duties of confidentiality on certain health care professionals not to disclose health information concerning patients.

The Model State Public Health Privacy Act addresses privacy and security issues arising from the acquisition, collection, maintenance, use, disclosure, and storage of identifiable health information by public health agencies at the State and local levels, including surveillance data. The Act attempts to protect identifiable, health-related information held by public health agencies against unwarranted uses and unauthorized disclosures without significantly limiting the ability of agencies to acquire and use such information for legitimate public health purposes. The present draft of the Act [as of 11/12/98] is divided into seven Articles with various sections and subsections (Table 1). Key provisions of the Act and their likely effect on establishing and maintaining an ARV therapy registry are included in the following sections of the Act and should be used as guidance in developing these systems.

Table 1

Key Provisions of the Model State Public Health Privacy Act		
Article I	1-103	Definitions
Article II	2-101	Acquisition of Public Health Information
	2-102	Duty To Hold Public Health Information Confidentially
	2-103	Individual Access to Public Health Information
	2-104	Accuracy of Information
Article III	3-101	Uses Consistent With Original Legitimate Public Health Purposes
Article IV	4-102	Least Intrusive Disclosures
	4-103	Posting of Written Protections
	4-105	Record for Disclosures
	4-106	Disclosures Without Informed Consent
	4-108	Disclosures With Informed Consent
	4-110	Secondary Disclosures
Article V	5-101	Duty To Hold Information Secure

Experiences of State HIV/AIDS Registries: New Jersey Department of Health and Senior Services

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In collaboration with
Mr. Samuel J. Costa, Ms. Pamela Costa, Ms. Gorney-Daley, and Dr. Suoqun Liu

New Jersey has the fifth highest prevalence of AIDS in the Nation with the highest cumulative AIDS cases in women (28 percent) and the third highest cumulative pediatric AIDS cases. Of the 695 total pediatric AIDS cases, 95 percent are perinatally acquired, and of the 367 pediatric HIV cases, 96 percent are perinatally acquired. Birth defects occur in 3 to 5 percent of total births (4,000 per year).

State laws and regulations pertaining to HIV/AIDS provide confidentiality for HIV/AIDS surveillance. State laws limit release of data without consent, reference Federal consent requirements, and issue civil penalties for infractions. State HIV/AIDS regulations include the reporting of HIV infection, as well as AIDS and CD4 counts, and exclude information from the public domain. There is a formalized surveillance security and confidentiality policy in place.

New Jersey has had named HIV reporting since October 1991. The collection of HIV/AIDS surveillance data in New Jersey is conducted through both passive and active surveillance. Both providers and laboratories passively report to the State. Active surveillance is conducted by the health department at a variety of sites. The HIV/AIDS registries also are matched with the vital statistics registry to ascertain births to HIV-infected mothers and also deaths of HIV-infected persons. To assess the implementation of PHS recommendations for perinatal HIV prevention, data are collected from prenatal, labor/delivery, neonatal, and pediatric charts.

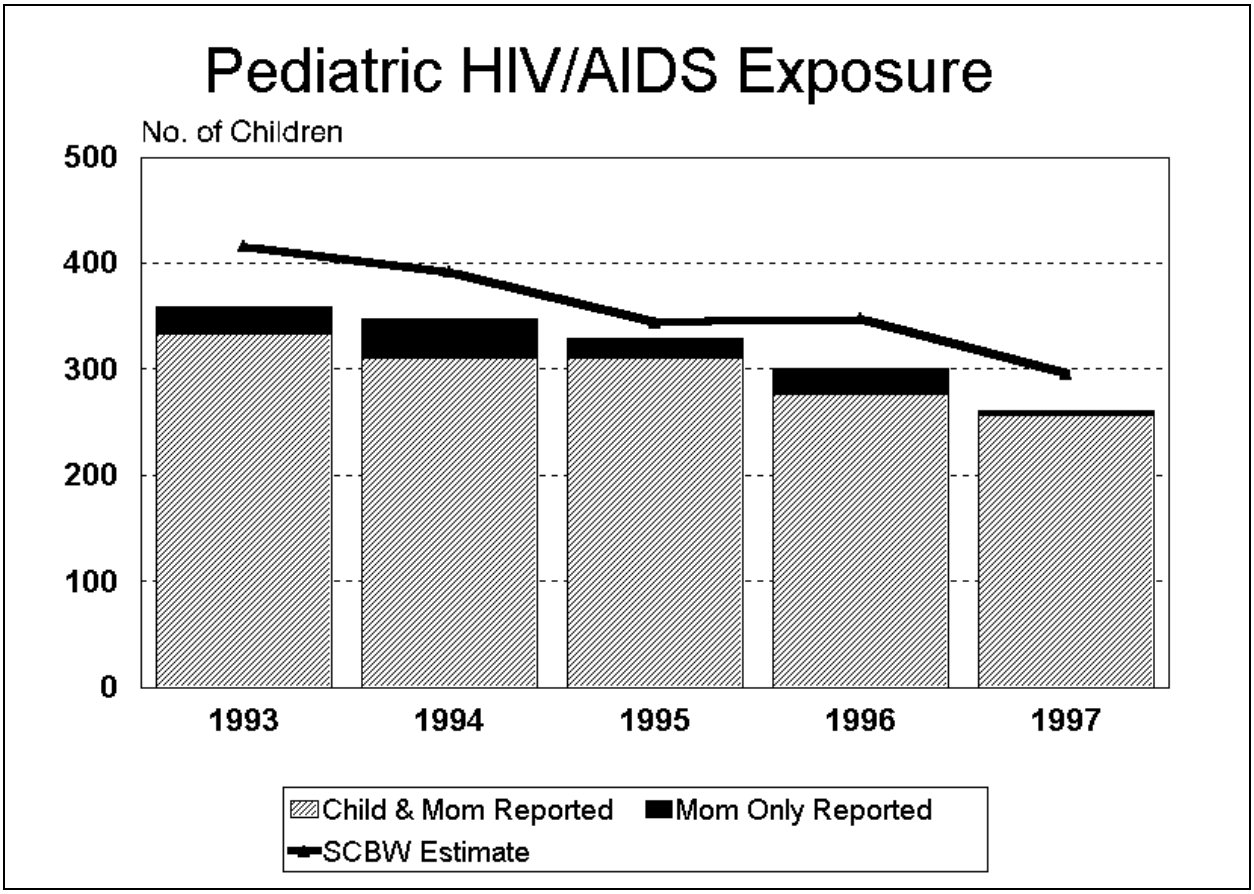
Data from HIV surveillance in New Jersey indicate very high ascertainment (95 percent) of mother/infant pairs each year compared to an anonymous survey of childbearing women that tests newborn blood spots for HIV antibody (Figure 1). Approximately 300 HIV-exposed babies are born each year in New Jersey, and this number has decreased slightly since 1993. The proportion of children who received ZDV during at least one of the three periods— prenatal, labor/delivery, or neonatal—increased from 8 percent in 1993 to 58 percent in 1997, and during that time, the proportion of infected children declined from 21 percent to 8 percent (Table 1).

The birth defects registry of New Jersey, established in 1928, is the oldest registry in the United States. Current laws and rules were implemented in 1985. Passive surveillance for birth defects is conducted by hospitals, providers, medical examiners, and cytogenetic laboratories (postnatal chromosome results). Active surveillance is in the form of annual audits that are conducted at all maternity hospitals and pediatric facilities with a reported 90 percent completeness. Reviews are conducted of all infant death certificates as well as of all deaths of 1- to 3-year-olds.

The Special Child Health Services (SCHS) registry conducts birth defect reporting and special needs reporting in two separate components. Birth defect reporting is State regulated and excludes information from the public domain. The special needs reporting is not mandatory but

historically has been emphasized. The focus of this special needs component is on children with noncongenital conditions.

Figure 1



The objectives of the match between the HIV/AIDS registry and the birth defects registry are to determine the feasibility of conducting such a match, to determine incidence of birth defects among perinatally HIV-exposed children who were exposed to antiretroviral agents *in utero* and compare this rate to the incidence of birth defects among infants perinatally exposed to HIV without exposure to antiretroviral agents, and to identify specific birth defects and their frequency in both of these groups.

The match was conducted with IRB approval and included 113,530 records from the SCHS registry (registration years 1985-1998) and 54,402 records from HIV/AIDS surveillance (cumulative to 11/30/98). The match required seven fields: name of the child, date of birth, sex, race, mother's Social Security number, county/city of residence, and date of death. Each match is then defined on a scale from 0 to 100, with a score above 70 signaling a good match, 50-70 a possible match, and less than 50 not a match. All possible matches are individually reviewed.

Preliminary results for the 1993-1998 birth cohorts show that of 538 cases of children exposed to antiretroviral treatment, 30 (6 percent) had birth defects compared to 82 (7.3 percent) of 1,131 children who were not exposed to ARV therapy or whose exposure information was not

available (Table 2). As a comparison, birth defects in the general population are 3 to 5 percent. Further analysis is pending.

In conclusion, these data demonstrate increasing use of the ZDV treatment regimen to prevent perinatal HIV transmission. These data also demonstrate that HIV/AIDS surveillance registries can be matched with birth defects registries and can help evaluate the relationship between perinatal exposure to antiretroviral therapy and birth defects on a systematic population-based basis.

Table 1

Pediatric HIV/AIDS Cases by Category

Birth Year	Infected	Indeterminate	Known Seroeverter	Total Reported	*Not Reported
1993	69 (21%)	78 (23%)	186 (56%)	333	26
1994	54 (17%)	111 (36%)	145 (47%)	310	38
1995	45 (15%)	97 (31%)	168 (54%)	310	19
1996	29 (10%)	102 (37%)	146 (53%)	277	24
1997	21 (8%)	150 (59%)	85 (33%)	256	5
1998	7 (4%)	170 (92%)	6 (3%)	183	17
Total	225 (13%)	708 (42%)	736 (44%)	1669	129

"Infected" includes HIV or AIDS. "Indeterminate" exposed children awaiting additional test results, or lost to follow-up. *Child under investigation.

Table 2

Pediatric Cases Born 1993-1998 in HARS: Preliminary Results Mother's AZT Use and Birth Defects

Mother received AZT during pregnancy or during labor/delivery	Birth Defect	No Birth Defect	Total
Yes	30 (6%)	508 (94%)	538 (100%)
No	39 (9%)	411 (91%)	450 (100%)
Unknown	43 (6%)	638 (94%)	681 (100%)
Total	112 (7%)	1557 (93%)	1669 (100%)

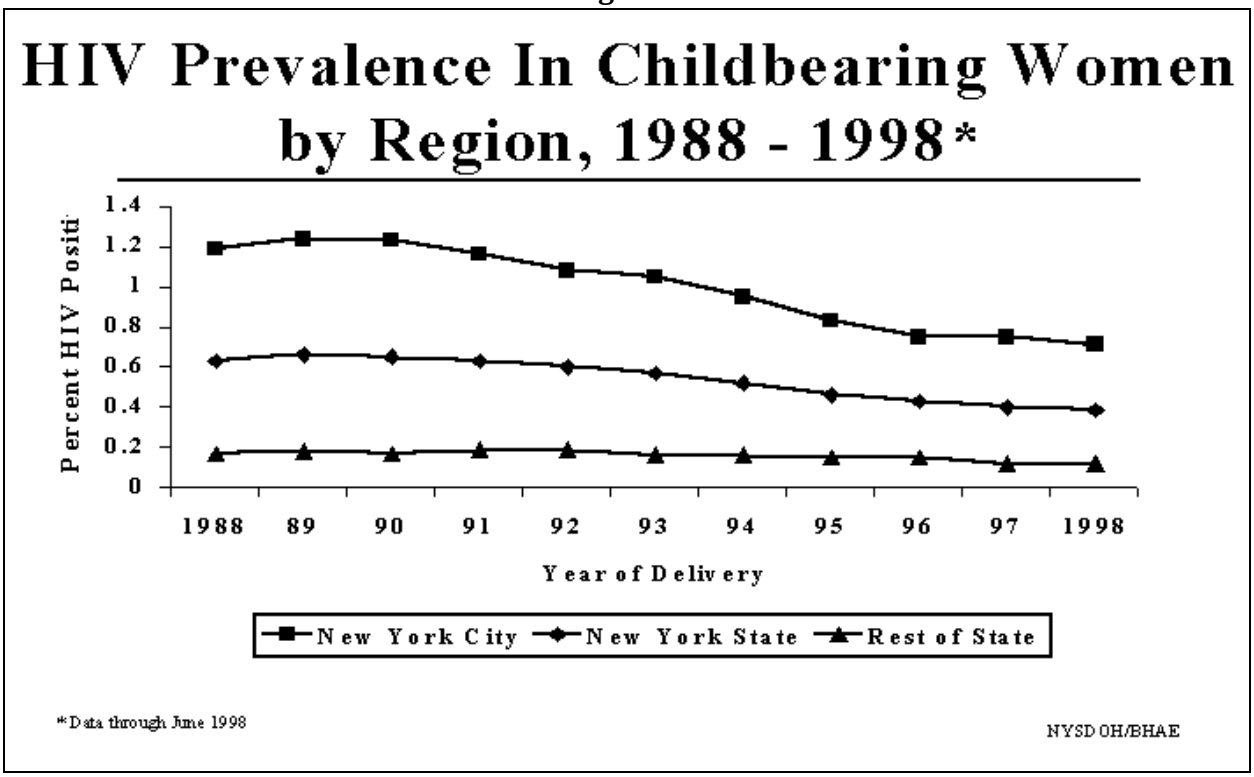
Experience of State HIV/AIDS Registries: New York State Department of Health

Dr. Guthrie S. Birkhead
New York State Department of Health

Dr. Birkhead described how prenatal and newborn HIV testing has evolved over time in New York. In November 1987, New York initiated the Survey of Childbearing Women (SCBW), which involved the blinded testing of all newborns that was unlinked to identifiers. This surveillance, which is estimated to be 96 percent complete, utilized leftover heel-stick metabolic screening specimens. The survey measures the exposure status of the infant and the infection status of the mother, allowing the health department to calculate the seroprevalence in childbearing women in the State. Using these methods, over 2.5 million tests have been performed.

HIV seroprevalence among childbearing women has declined 41 percent from 1989 (0.66 percent) to 1998 (0.39 percent). This decline, however, was not uniform across demographic and geographic groups (Figure 1). The decline could be due to the aging of the initial cohort of infected women or to the possibility that fewer HIV-infected women are becoming pregnant.

Figure 1



From May 1996 to January 1997, State regulations required prenatal counseling with recommended testing in regulated settings. Additionally, all women were counseled at delivery and offered newborn HIV testing. Consent was noted on the newborn screening form. If consent

was not granted, blinded testing continued. During this program, 90 percent of the women consented and results were returned for 567 HIV-seropositive women (70.3 percent).

In February 1997, New York State legislation declared effective the Comprehensive Newborn HIV Testing Program. This law continued mandatory prenatal counseling in regulated settings, but also required HIV testing for all newborns and for the test results to be returned. HIV-seropositive newborns were followed until diagnostic polymerase chain reaction (PCR) test results were received; specialized care centers were made available for these newborns.

Data collected in New York to monitor perinatal HIV prevention include the newborn screening data, such as mother's and newborn's names, address, and pediatric care provider as well as followup PCR results. The program is monitored by reviewing medical records, including the prenatal, intrapartum, newborn, and pediatric medical charts, on all HIV-seropositive births. Data are collected on counseling and testing during prenatal care, ACTG 076 protocol administration, other maternal antiretroviral therapy, HIV infection status of the newborn, appropriate medical care for newborns pending the determination of their infection status, and antiretroviral therapy for infected newborns.

In New York, there are data on HIV-seropositive newborns with identifiers and their medical data as outlined above on 578 children born in 1996 through the consented program, and along with 958 children born in 1997 and 872 born in 1998 through the comprehensive testing program. Possible purposes for maintaining these data are to conduct etiologic studies and to notify persons at risk if any future screening recommendations are developed, e.g., cancer screening.

Potential followup studies for New York State include matching the HIV-seropositive births to (1) the New York State Congenital Malformations Registry, which was established in 1982 and has 9,455 reports from 1982 to 1994, and (2) the New York State Cancer Registry, which has provided successful matches to the AIDS Registry in the past and is not a SEER registry.

Dr. Birkhead concluded with pertinent issues for public health agencies to consider:

- Obligation of public health agencies to consider followup studies if they possess data that could help answer these questions;

- Need to use the IRB process in considering studies to protect individuals involved;

- Examination of current legal basis and seeking specific legal authority if needed;

- Consideration of establishing a complete database of exposed children, e.g., retrospective enrollment, especially if long-term notification is a goal;

- Cooperation across jurisdictional lines to ensure comparable methods; and

- Need for funding for these activities.

Experiences of State HIV/AIDS Registries: Michigan Department of Community Health

Ms. Eve Mokotoff
Michigan Department of Community Health
In collaboration with Ms. Hollie Malamud and Ms. Linda Scott

Active HIV/AIDS surveillance in Michigan involves solicitation of case reports. Michigan has conducted active AIDS surveillance since 1986 and active HIV surveillance since 1992. Reports for HIV infection are obtained from providers, death certificates, birth certificates, laboratories, obituaries, etc. Most HIV infection is reported confidentially, but the anonymous option is available. Michigan public health code states the following: "All reports, records and data pertaining to testing, care, treatment, reporting, and research associated with the serious communicable diseases or infections of HIV infection, AIDS, and ARC [AIDS-related complex] are confidential and shall be released only pursuant to this section."

Michigan is considered a medium HIV prevalence State with approximately 10,000 cumulative AIDS cases and an estimated 12,500 persons currently living with HIV/AIDS. Compared to the other States/territories, Michigan ranks 17th based on the number of AIDS cases and 31st based on the annual AIDS rate per 100,000 population. Of the persons currently living with HIV/AIDS in Michigan, 21 percent are female, 58 percent are black, 37 percent are white, 3 percent are Hispanic, 43 percent are men who have sex with men, 21 percent are injecting drug users, and 11 percent are heterosexual. Among perinatal exposure cases, 224 are currently alive, of whom 75 percent are black, 19 percent are white, 4 percent are Hispanic, and 69 percent are residents of the tri-county area surrounding Detroit. The remaining perinatal exposure cases are found in 20 of Michigan's 83 counties. The 1996 Ryan White Comprehensive AIDS Resources Emergency Act (RWCA) reauthorization requires followup of all HIV-exposed children.

Michigan prenatal testing law requires that pregnant women must be offered counseling and testing for HIV, hepatitis B virus, and other sexually transmitted diseases at the time of the first prenatal visit. HIV testing of pregnant women and their infants is voluntary. Written, informed consent for testing must be obtained prior to testing and documented in the patient's medical records. Michigan law states that testing may not be performed if it is medically inadvisable or the client refuses consent, and women with no prenatal care must be offered the above-mentioned counseling and testing. Women who test positive must not be denied care or services and cannot be reported to Child Protective Services based on HIV-seropositive status.

The Study to Evaluate the Prevention of Perinatal HIV Transmission (STEP), which involves Louisiana, Michigan, New Jersey, and South Carolina, is part of ongoing pediatric surveillance. The objectives of STEP are as follows:

- To measure the percentage of HIV-seropositive women giving birth each year who know their infection status before delivery;

- To measure the percentage of individuals who received ZDV prenatally, intrapartum, and postnatally (newborn);

- To identify and characterize populations and health care settings where prenatal ZDV is less utilized;

- To determine the transmission rate among children born to these women; and

- To monitor for short- and long-term adverse effects.

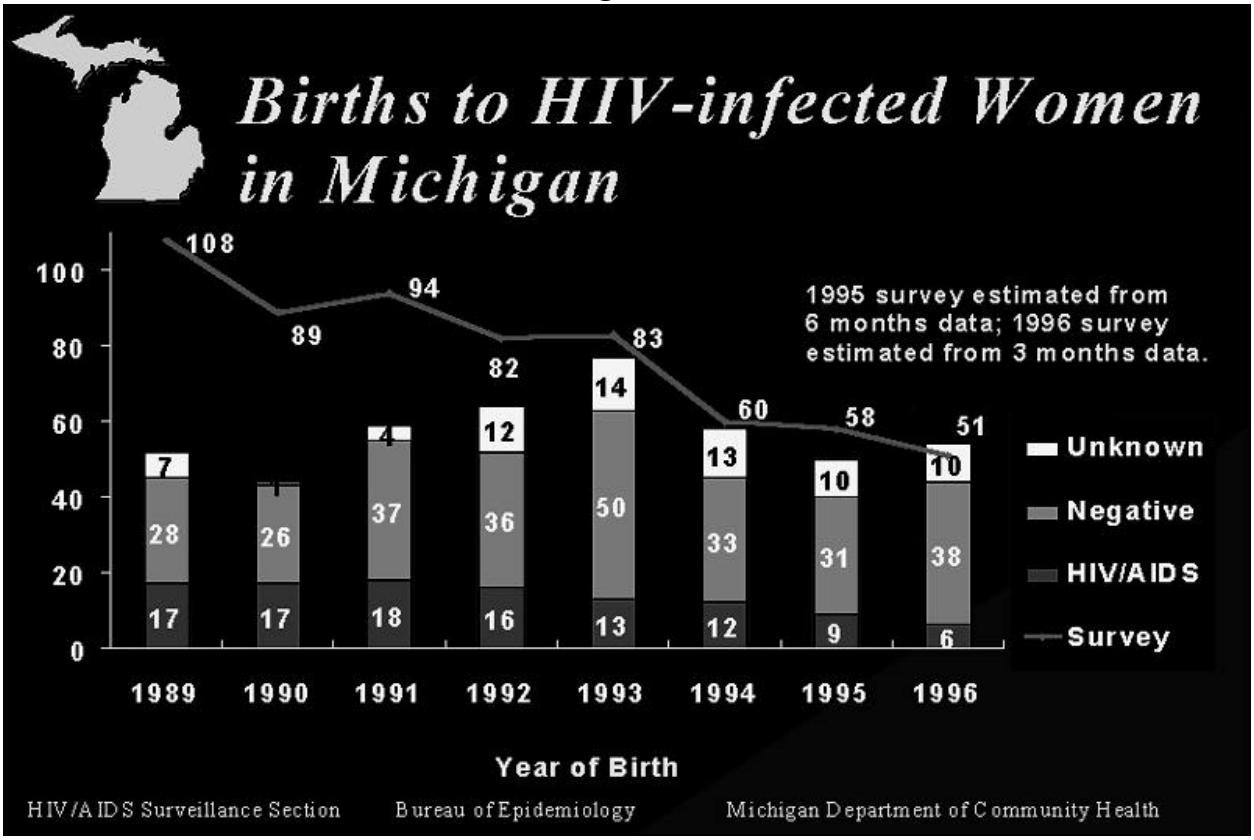
Mother-baby pairs are found from active case finding at larger obstetric hospitals, annual matching of HIV/AIDS registries with birth registries to find babies born to mothers already in the registry, and HIV/AIDS surveillance. The surveillance also covers women pregnant at the time of report and matches (un)reported mothers with (un)reported children. The charts reviewed to obtain this information include the prenatal care record, labor and delivery record, newborn record, ongoing pediatric medical record, and the mother's HIV clinical record. Other information obtained through this surveillance program includes information on ZDV treatment, transmission risk, other children, etc. Many of the STEP activities are now part of ongoing pediatric surveillance. Although the number of children born to HIV-infected women is decreasing, this pediatric surveillance is labor intensive and needs explicit funding. These studies have been published recently in *Morbidity and Mortality Weekly Report*, 1998; 47, No. 33: "Success in Implementing Public Health Service Guidelines to Reduce Perinatal Transmission of HIV—Louisiana, Michigan, New Jersey, and South Carolina, 1993, 1995, and 1996."

In Michigan, the proportion of HIV-infected women tested for HIV before their child's birth increased over time to over 90 percent in 1996. Prenatal ZDV use increased from 7 out of 64 (11 percent) births in 1992 to 44 out of 54 (81 percent) in 1996; intrapartum ZDV use increased from 4 of 64 (6 percent) to 41 of 54 (76 percent). Neonatal (within 72 hours of birth and for the first 6 weeks of life) ZDV use increased from 4 out of 64 (6 percent) in 1992 to 48 out of 54 (89 percent) in 1996. Additionally, 9 out of 64 (14 percent) of HIV-exposed children born in 1992 developed HIV infection, while this number decreased to 4 out of 54 (7 percent) by 1996. Two out of the 64 (3 percent) HIV-exposed infants in 1992 were diagnosed with AIDS within 1 year of birth; in 1996, this number was 3 out of 54 (6 percent).

HIV prevalence may be higher in women who lack prenatal care. It was found that the vast majority of perinatally exposed babies who become HIV-infected were born to women who did not receive prenatal care. A small number received prenatal care but were not offered or refused HIV testing. Drug use history, drug-using partners, and ongoing high-risk behaviors during pregnancy are risk factors for women less likely to receive prenatal care. It is recommended that women with known ongoing high-risk behaviors during pregnancy should be offered retesting if negative on initial screening. There was a small number of women who received prenatal care but were not offered or refused testing.

Figure 1 summarizes the trends identified by this surveillance program. Births to HIV-infected women also have declined in Michigan overall. In addition, an increased number of HIV-infected pregnant women are being given ZDV prophylaxis, an increased number of HIV-exposed infants are being given ZDV prophylaxis as neonates, and fewer children are becoming infected with HIV perinatally.

Figure 1



The Birth Defects Registry in Michigan, currently with 700-800 children registered, began in 1992 for births since 1990 for children under 2 years of age. In 1999, this will change to under 1 year of age to be consistent with other States. The information is sent to the State health department, usually electronically, from cytogenetic laboratories, clinics, and hospitals. The registry has yet to be evaluated, but Michigan data are comparable to those of other States. The match with the HIV/AIDS registry will be the first link for the birth defects registry. In the birth defects registry, personal identifiers are collected for each case to minimize duplication and to match cases to birth/death files along with other pertinent databases. Personnel with access to the database are bound by State laws mandating confidentiality, which is ensured by MCL 333.2631.

The Cancer Registry in Michigan was established in 1984 to tabulate cancer incidence rates for the State and to permit epidemiologic research. The individual cancer reports in the registry, recorded and sent by hospitals and clinical laboratories, numbered over 600,000 by the end of 1995. Included in this Statewide registry are data reported by the Southeast Michigan SEER registry. SEER places abstractors at the hospitals to collect incident cancers for the tri-county area surrounding Detroit. These cancer reports are afforded confidential handling as required by State law and by administrative rule. Information may be provided to a researcher conducting approved research. The match of the cancer registry to the HIV/AIDS registry was approved last year by the scientific advisory panel that reviews requests to use the cancer registry for research. This panel reviews the confidentiality protections as well. These population-based evaluations are

feasible and could provide additional information on the potential toxicities of ARV drug exposure during pregnancy.

Using Administrative (Medicaid) Data To Assess ZDV Use and Birth Defects

Dr. C.J. Newschaffer
Thomas Jefferson University
In collaboration with J. Cocroft, C.E. Anderson, W.W. Hauck, and B.J. Turner

Medicaid databases contain complex series of recipient, provider, and claims processing files designed to track financial rather than medical data. Clinical information is derived from ICD-9-CM diagnosis and procedure codes and State-specific codes contained in the databases. The Medicaid programs that provide health insurance to the indigent differ from State to State.

When using Medicaid data for epidemiologic research, three major issues must be addressed:

1. External validity: Is the group under study representative of the population of interest?
2. Internal validity: Are the observed associations real?
3. Responsiveness/cost of research.

Dr. Newschaffer reviewed the strengths and weaknesses of Medicaid data for studies of antiretroviral therapy and birth defects, discussed the means of addressing possible pitfalls, and provided an example using data from one State. He highlighted the strengths and weaknesses of Medicaid databases for investigating ARV therapy and birth defects as seen in Table 1.

Table 1

	Medicaid Databases	**Example Analysis**
External validity	++	
Internal validity		
Selection bias	+	
Information bias	--	√
Confounding	--	√
Precision		
Responsiveness/Cost	++	

Using Medicaid databases for investigating antiretroviral treatments and birth defects was more externally valid since Medicaid overrepresents persons of low socioeconomic status, women, children, and nonwhite ethnic groups, and the majority (>80 percent) of HIV-infected pregnant women are covered by Medicaid.

To assess internal validity, the use of Medicaid databases must be evaluated in several categories.

1. Selection biases—Use of Medicaid databases is found to be mostly valid because they generally allowed for less selection. There was some selection present because mothers were not linked to children, and there could have been errors in HIV serostatus ascertainment.

However, the magnitude of this selection was not differential or high: an HIV Status Validation substudy revealed a sensitivity of 93 percent and specificity of 97 percent. Additionally, some statistical adjustment is possible.

2. Information bias, which could affect misclassification of ARV drug exposure—Use of Medicaid databases is potentially a good source for drug exposure data. Both clinical trials and pre-eligibility use could not be detected on the Medicaid database, as women with <100 percent eligibility (n=719) and women with encounters at known clinical trial sites (n=581) are excluded. Additionally, to determine the trimester of first exposure, the date of conception must be back-calculated. Misclassification is further complicated by the concern with false positives (poor positive predictive value for central nervous system defects) and false negatives. Surveillance bias also is a source of information bias, e.g., children of women receiving ART may be followed longer/better for birth defects.

3. Confounding—Medicaid databases do not include information on certain confounders, which is a potential problem.

4. Precision/Sample Size—Because rare events are best studied in large populations, Medicaid data may be useful as it is comparably easier to assemble large study populations using these data.

5. Responsiveness and cost—Use of existing Medicaid databases for investigating ARV therapy and birth defects due to the retrospective cohort designs may be less expensive data in comparison to primary data collection. Additionally, State Medicaid officials link databases and create “deidentified” files.

An illustrative analysis was conducted on 1,932 deliveries from January 1993 to September 1996 to HIV-infected women on New York State Medicaid (Figures 1-3). Adjusted odds ratios (AORs) were estimated of any major birth defect for any ZDV exposure during pregnancy, and ZDV by trimester of first exposure. Covariates in the data include age, race, education parity, alcohol use, smoking, substance abuse, low birth weight, and observation time. Data were collected with and without sample restrictions (Figures 1-3).

In conclusion, there was no evidence of association with first-trimester exposure. The overall association of any exposure was driven by late pregnancy exposure and is still open to further evaluation in terms of biological plausibility, chance variation, and surveillance bias. Medicaid data have proven to be useful when analyzing large numbers of persons, and many data pitfalls can be addressed. This utility can be further improved through more linkage and validation, for example, with medical records and the congenital malformation registry.

Figure 1

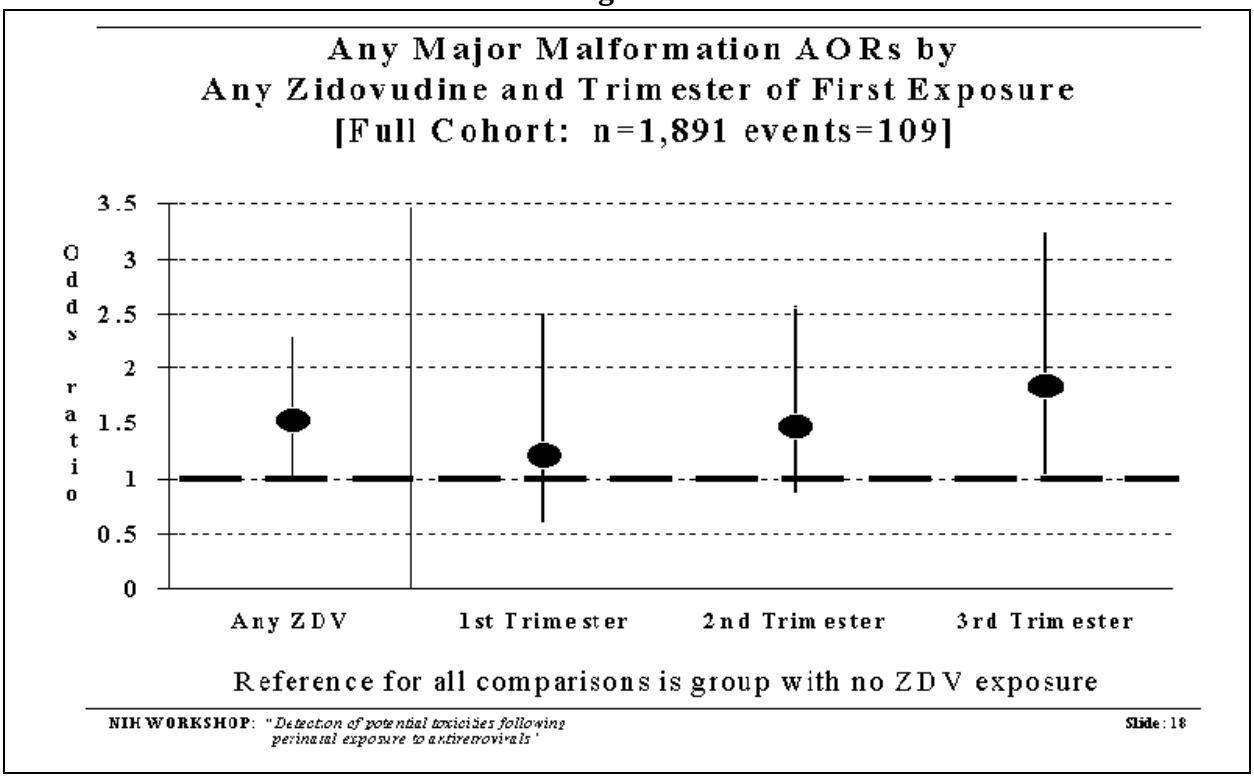


Figure 2

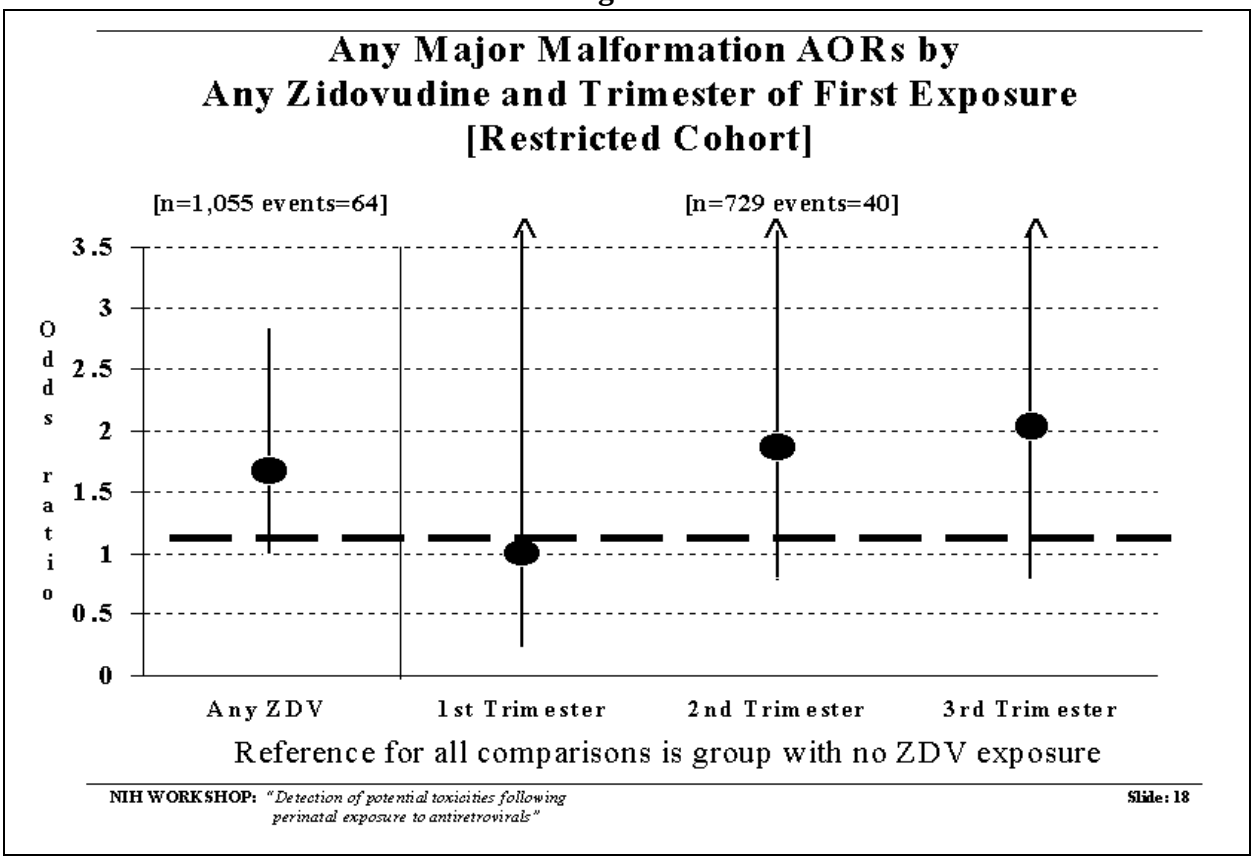
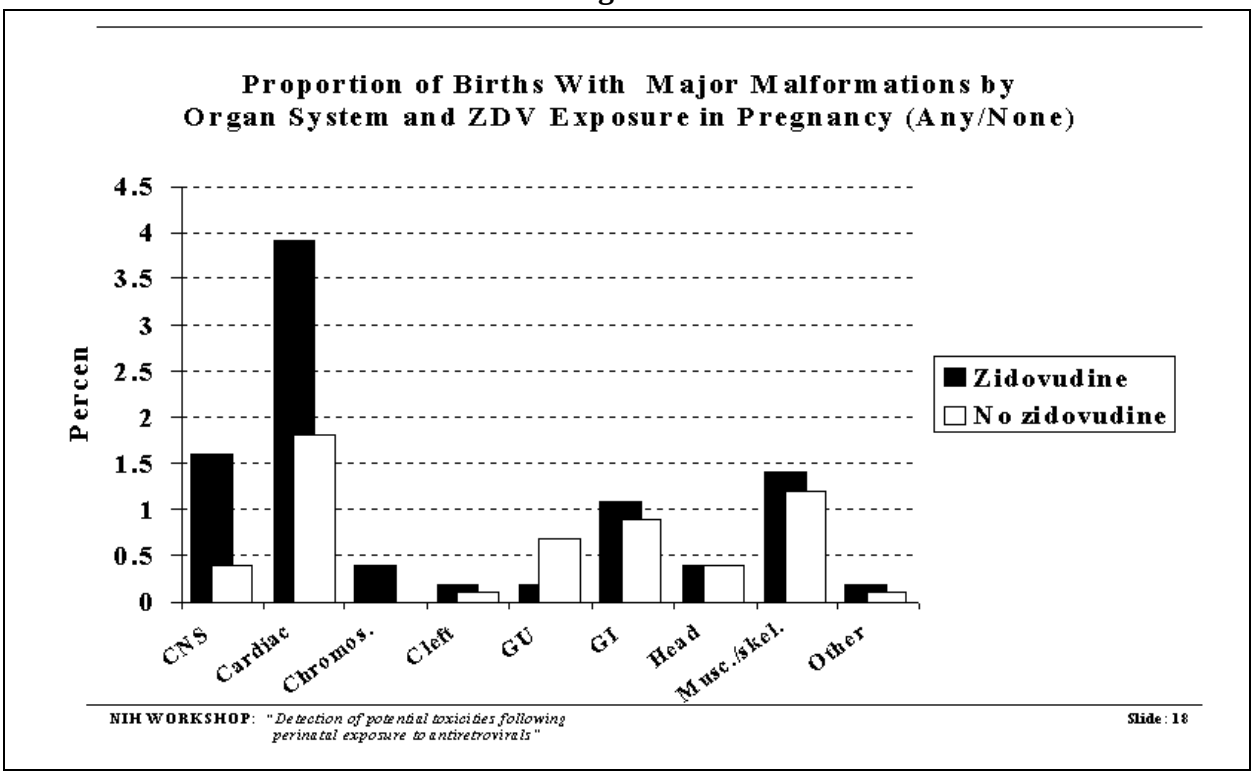


Figure 3


Proportion of Births With Major Malformations by
Organ System and ZDV Exposure in Pregnancy (Any/None)
Percen
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
CNS
Cardiac
Chromos.
Cleft
GU
GI
Head
Musc./skel.
Other
Zidovudine
No zidovudine
NIH WORKSHOP: "Detection of potential toxicities following perinatal exposure to antiretrovirals"
Slide: 18

Appendix V

Glossary

ACTG	AIDS Clinical Trials Group
AIDS	acquired immunodeficiency syndrome
AOR	adjusted odds ratio
APR	Antiretroviral Pregnancy Registry
ARC	AIDS-related complex
ART	antiretroviral therapy
ARV	antiretroviral
ATLL	adult T-cell lymphoma/leukemia
AZT	azidothymidine (also known as ZDV)
BRFS	Behavioral Risk Factor Survey
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CPP	Collaborative Perinatal Project
CSTE	Council of State and Territorial Epidemiologists
ddC	dideoxycytidine
ddI	dideoxyinosine
DES	diethylstilbestrol
d4T	stavudine
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
FDA	Food and Drug Administration
FOIA	Freedom of Information Act
GAZT	glucuronide form of AZT
HAART	highly active antiretroviral therapy
HARS	HIV/AIDS Reporting System

HCUP	Healthcare Cost and Utilization Project
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HMO	health maintenance organization
HPRT	hypoxanthine phosphoribosyl-transferase
HRSA	Health Resources and Services Administration
HSR	human subjects research
HTLV-I	human T-cell lymphotrophic virus type I
IRB	institutional review board
MIRIAD	Mother-Infant Rapid Intervention at Delivery
NADH	nicotinamide adenine dinucleotide
NCI	National Cancer Institute
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Study
NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
OI	opportunistic infection
OR	odds ratio
PACTG	Pediatric AIDS Clinical Trials Group
PACTS	Perinatal AIDS Collaborative Transmission Study
PCR	polymerase chain reaction
PHS	Public Health Service
PSD	Pediatric Spectrum of Disease
RR	relative risk
RWCA	Ryan White Comprehensive AIDS Resources Emergency Act
SCBW	Survey of Childbearing Women
SCHS	Special Child Health Services
SEER	Surveillance, Epidemiology, and End Results

STEP	Study to Evaluate the Prevention of Perinatal HIV Transmission
3TC	lamivudine
WITS	Women and Infants Transmission Study
ZDV	zidovudine (also known as AZT)